KINETIC STUDIES

OF

PLATINUM COMPLEXES

A thesis submitted in partial fulfilment of the requirements for the degree of

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Most people say that it is the intellect which makes a great scientist.

They are wrong, it is the character.

Albert Einstein 1879 - 1955

ABSTRACT

Since the chance discovery, in 1967, of the anti-tumour activity of cisplatin, *cis*-dichlorodiammineplatinum(II), research has focussed on studying the reactions of this and other related complexes in an effort to elucidate the nature of the biological activity. This thesis presents a study of the aqueous solution chemistry of some platinum(II) and platinum(IV) complexes in order to extend what is known about the simple chemistry of this biologically important class of compounds.

The chloride ion anation of diaqua (*cis*-$[Pt(OH_2)_2(N)_2]^{2+}$) complexes is investigated as is the bromide ion anation of the bromoaqua (*cis*-$[PtBr(OH_2)(N)_2]^{+}$) and diaqua (*cis*-$[Pt(OH_2)_2(N)_2]^{2+}$) species, all in 1.0 M $HClO_4$. The kinetics are studied using UV/Vis spectroscopic methods - both conventional and stopped-flow. High-pressure stopped-flow is used for selected reactions to determine the effect of pressure on the anation process. The collective data are used to calculate activation parameters from which conclusions are drawn as to the mechanism of the reaction.

The redox kinetics of the platinum(II)/platinum(IV) couple are investigated using a variety of redox agents. These data provide a basis on which to form mechanistic interpretations for both the oxidation and reduction processes. Extrapolations are made to the biological system for the reduction of anti-tumour active platinum(IV) drugs.

Platinum(IV) complexes are known to be very inert. An investigation into the base hydrolysis of platinum(IV) complexes is presented and a mechanism proposed.

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ABBREVIATIONS

cis-$(NH_3)_2$	*cis*-$[PtCl_2(NH_3)_2]$
trans-DDP	*trans*-$[PtCl_2(NH_3)_2]$
trans-$(NH_3)_2$	*trans*-$[PtCl_2(NH_3)_2]$
en	$NH_2CH_2CH_2NH_2$
tn	$NH_2CH_2CH_2CH_2NH_2$
Me_2tn	$NH_2CH_2C(CH_3)_2CH_2NH_2$
chxn	cyclohexanediamine
cis-$(py)_2$	*cis*-$[PtCl_2(pyridine)_2]$
d(pGpG)	deoxy(phosphate-guanine-phosphate-guanine)
d(pApG)	deoxy(phosphate-adenine-phosphate-guanine)
diaqua	*cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$
monoaqua	*cis*-$[PtCl(NH_3)_2(OH_2)]^{+}$
bromoaqua	*cis*-$[PtBr(NH_3)_2(OH_2)]^{+}$
DMF	dimethylformamide

PUBLICATIONS

1. K. Hindmarsh and D.A. House, An easily demonstrated zero-order reaction in solution., *J. Chem. Ed.*, **73** (1996) 585.

2. K. Hindmarsh, D.A. House and M.M. Turnbull, The hydrolysis products of *cis*-diamminedichloroplatinum(II). 9. Chloride and bromide anation kinetics for some $[Pt^{II}(N)_2(OH_2)_2]^{2+}$ complexes and the structures of $[Pt^{IV}Br_4(N)_2]$., *Inorg. Chim. Acta*, **257** (1997) 11-18.

3. K. Hindmarsh, D.A. House and R. van Eldik, The redox chemistry of platinum complexes., *Inorg. Chim. Acta.* Manuscript accepted.

4. K. Hindmarsh, D.A. House and R. van Eldik, The hydrolysis products of *cis*-diamminedichloroplatinum(II). 10. Activation volumes for halide aquation and anation processes. Manuscript in preparation.

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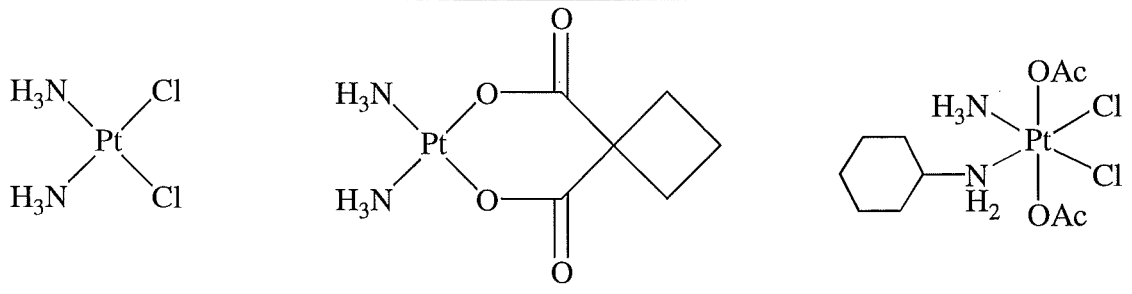
CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

The discovery, in 1965, that a platinum coordination complex, *cis*-diamminedichloro-platinum(II) (cisplatin, cis-DDP), was an anti-tumour agent led to a resurgence of interest into the chemistry of platinum complexes. Cisplatin is currently one of the most widely used anti-cancer drugs in the USA with 30,000 patients undergoing successful treatment each year [1]. It is used mainly for treating testicular and ovarian cancer but tumours of the bladder, head, neck and lungs are also sensitive to treatment [2 - 3]. The advent of cisplatin has increased the long term survival rate (defined as the cancer not returning within 5 years) for men suffering from testicular cancer to greater than 85 % [4].



cisplatin carboplatin JM-216

Figure 1.1: Platinum-based anticancer drugs.

1.2 DISCOVERY OF CISPLATIN

The first indication that platinum-based coordination compounds could be used in cancer chemotherapy came from a chance discovery by Barnett Rosenberg in 1965 [5]. He was investigating the effects of an electric field on growth processes in bacteria, specifically *Escherichia coli*, by passing an electric current through platinum electrodes immersed in a nutrient medium consisting of NH_4Cl, Na_2HPO_4, KH_2PO_4, NaCl, $MgCl_2$ and Na_2SO_4 ('C' medium). As a result, bacteria formed long filaments up to 300 times their normal size implying that although cell growth was not affected, cell division was inhibited. Further experiments showed that it was not the current causing bacterial elongation, but rather a new long-lived chemical species produced when the 'inert' platinum electrode dissolved electrolytically in the nutrient medium [6]. Analysis of the solution showed that the platinum species formed in solution was $[PtCl_6]^{2-}$ which acting as a bactericide, inhibited cell growth at concentrations of 10 ppm. It was later observed by van Camp that aged solutions of $(NH_4)_2[PtCl_6]$ (2 - 3 days old) produced filamentous bacteria at very low platinum concentrations [7]. Further investigation showed that the platinum-containing components in solution could undergo a photochemical reaction to produce $[PtCl_5(NH_3)]^-$. This species neither affected cell growth nor cell division but it readily converted to the more stable neutral $[PtCl_4(NH_3)_2]$ complex, which was a potent inhibitor of cell division whilst having little effect on bacterial growth [7]. This platinum(IV) compound exists in two isomeric forms, *cis*- and *trans*-$[PtCl_4(NH_3)_2]$, but testing of the two isomers showed that while the *cis* form had biological activity, the *trans* form had little effect on cell division. At the same time the corresponding platinum(II) complexes were synthesised and again, the *cis* form was active and the *trans* form inactive. These platinum(II) species are produced, in

small quantities, from the spontaneous thermal reduction of the corresponding $[PtCl_4(NH_3)_2]$ isomers [8].

Another aspect of the bacterial activity was reported by Reslova *et al* [9]. They found that lysogenic strains of *E. coli* can be induced by the platinum compounds, to develop partial or complete viruses leading to destruction (lysis) of the cell. This effect can also be caused by other agents such as UV, X-rays and chemicals such as nitrogen mustards and other anti-tumour agents [10].

It was subsequently suggested that these platinum compounds be tested for anti-tumour activity due to their ability to inhibit cell division but not cell growth. This suggestion was further reinforced by the fact that other anti-tumour agents, including alkylating agents and actinomycin D, were also observed to cause elongation and lysis in lysogenic bacteria [8]. Initially four compounds were tested against Sarcoma 180 in the ICR strain of mice: *cis*-$[Pt^{IV}Cl_4(NH_3)_2]$, *cis*-$[Pt^{II}Cl_2(NH_3)_2]$, $[Pt^{II}Cl_2(en)]$ and $[Pt^{IV}Cl_4(en)]$. All four were found to be effective in inhibiting tumour growth [11] but the corresponding *trans* isomers were ineffective, as predicted by the bacteriological results. Further testing showed *cis*-$[Pt^{II}Cl_2(NH_3)_2]$ to be the most potent of the four complexes tested initially [12] and it was submitted (1971) for subsequent screening to the National Cancer Institute of America.

Cis-$[PtCl_2(NH_3)_2]$, *cis*-diamminedichloroplatinum(II), cisplatin or cis-DDP, was not a new compound. It had been first synthesised in 1845 and was known as 'Peyrones Chloride' [13]. The existence of the *cis* and *trans* isomers had been established by Werner in 1890 [14] and the crystal structure of the *cis* isomer was determined by Milburn in 1966 [15].

Phase 1 clinical trials of cisplatin began in 1971 [2] and despite having a broad range of toxic side-effects it showed marked activity against advanced testicular and ovarian cancer [16]. The dose-limiting side-effect was nephrotoxicity but patients also experienced very intense nausea and vomiting. In addition to these, loss of hearing and neurotoxicity were also observed in some patients. In 1973 doubts were expressed as to whether cisplatin would ever be used as an anti-tumour agent due to its extreme toxicity [17]. A major breakthrough came in 1977 with the technique of hydrating the patient before and after treatment using D-mannitol, an osmotic diuretic agent [18]. This minimised the concentration of the complex in the kidneys and allowed higher doses to be given (up to 300 % greater) while decreasing the kidney toxicity. Other advances came by introducing anti-emetics such as 5-HT_3 antagonists to reduce the intense nausea and vomiting [17] and by infusing the drug slowly over 6 - 8 hours to keep the concentration of cisplatin in the kidneys to a minimum [19].

During this same period in the 1970's, studies showed that when cisplatin was combined with other anti-tumour agents a substantial improvement in the effectiveness of the treatment was seen [20 - 21]. Two such drugs are bleomycin and vinblastine. These combinations proved extremely successful in treating cancers of the genito-urinary type (testicular and ovarian) [19, 22] and marketing approval for cisplatin was obtained in the USA for its sale under the trade name 'Platinol' in 1978. International registration of the drug followed with approval in the UK in 1978 and in Japan in 1984 [17].

1.3 DEVELOPMENT OF PLATINUM-BASED ANALOGUES

Although cisplatin was seen as a 'wonder drug' it had limitations due mainly to its side-effects. It was also not effective in the treatment of colorectal (bowel) and breast tumours – two of the most prevalent types of cancer. This lead to a search for platinum-based analogues with similar or better clinical activity and lower toxicity, as well as a broader spectrum of activity. Many thousands of platinum(II) and platinum(IV) compounds have been synthesised and tested for anti-tumour activity and from this certain structural requirements were elucidated in the 1970's [23 - 26].

- The complex should be electrically neutral even though the active form may be charged after undergoing ligand-exchange processes. The drug must be neutral in order to pass across biological membranes [9]. Charged species may also be quite toxic [27].
- Two *cis* monodentate leaving groups are required.
- The leaving groups, usually anions, should have groups with intermediate binding strength to platinum(II) (eg. chloride). Labile complexes will react too rapidly and indiscriminately thus preventing the drug from reaching the tumour site. Inert complexes will not react significantly enough to elicit a response.
- The amine ligands, either monodentate (eg. NH_3) or bidentate (eg. ethylenediamine) should have a *cis* configuration, be relatively inert and have at least one N-H group. All complexes tested not containing this functionality were inactive [4, 28] and it is thought that this N-H moiety may be important in the interaction of cisplatin with DNA.

- Most of the initial platinum complexes that have proven to be anti-tumour active have had platinum in the +II oxidation state. However, Tobe *et al* found that the oxidation state was not critical [29] and indeed, the initial platinum complex found to be active was *cis*-$[Pt^{IV}Cl_4(NH_3)_2]$ [7].

These requirements hold in many cases but, as with most things, there are exceptions to the rules and so the above criteria need not be valid for every platinum drug available. Indeed, the more recent analogues defy all the structure-activity relationships with *trans* drugs showing activity when platinum is coordinated to a large ligand eg. pyridine. However, these drugs may interact with DNA in a different manner to cisplatin [118].

There are also certain requirements that were thought necessary in the design of new anti-tumour drugs in order to improve their efficiency.

- Activity in tumours that are resistant to cisplatin and improved activity in cancers that respond to cisplatin.
- Reduced toxicity, and treatable side-effects.
- Improved physical properties such as greater aqueous solubility, solution stability and longer lasting action.

The development of these structure-activity relationships resulted in the synthesis of an extraordinary number of platinum compounds all of which were tested for their anti-tumour activity. From the complexes tested, 23 were found to be suitable for clinical trials. Only one of these second-generation platinum drugs, carboplatin, is now being routinely used for treatment of tumours [17].

Carboplatin, 1,1-cyclobutanedicarboxylatodiammineplatinum(II) (Figure 1.1), has a similar clinical activity to cisplatin with minimal toxicity to the kidneys,

hearing, nervous and gastrointestinal systems. The dose-limiting feature of carboplatin is myelosuppression (suppression of bone marrow production) which can be muted using haematopoietic growth factors. These growth factors promote the production of the white blood cells necessary for the immune system to function. The slower hydrolysis of the cyclobutanedicarboxylate ligand results in the lower toxicity of carboplatin [21, 30, 145]. Carboplatin is limited in that it shows cross-resistance with cisplatin and thus it also has a limited spectrum of cancers against which it is active.

Further analogues of cisplatin currently under clinical testing fall into two main categories. Firstly there are the 1,2-diaminocyclohexane (dach, chxn) derivatives (ormaplatin, tetraplatin, oxaliplatin, L-NDDP) whose development has been based on their non-cross-resistance in cisplatin resistant murine leukemias. The second category is carboplatin analogues (zeniplatin, enloplatin, lobaplatin) with either cyclobutanecarboxylate or other oxygen-containing leaving groups [31].

Burchenal *et al* [32 - 33] originally observed that a series of analogues containing a diaminocyclohexane moiety had activity against a cisplatin-resistant cell line. They found that the *in vitro* activity of these chxn derivatives was independent of the leaving group. Ormaplatin [21] is a 1,2-chxn complex that is of interest due to its broad spectrum of activity and ability to overcome cisplatin resistance. It has associated with it strong neurotoxicity which may be overcome by use of agents such as Org-2766, a protectant against cisplatin neurotoxicity.

Tetraplatin (Figure 1.2) is a racemic mixture of [$PtCl_4${(±)-*trans*-chxn}]. This platinum(IV) complex is rapidly reduced in tissue cultures and *in vivo* to the platinum(II) species [$PtCl_2${(±)-*trans*-chxn}] [34]. Tetraplatin has a similar spectrum

of activity to cisplatin with the exception of the lack of cross-resistance to the L1210 and P388 leukemias. Emesis and myelosuppression have been reported but these are less severe. Hydration therapy must still be used and the main side-effect appears to be peripheral sensory neuropathy.

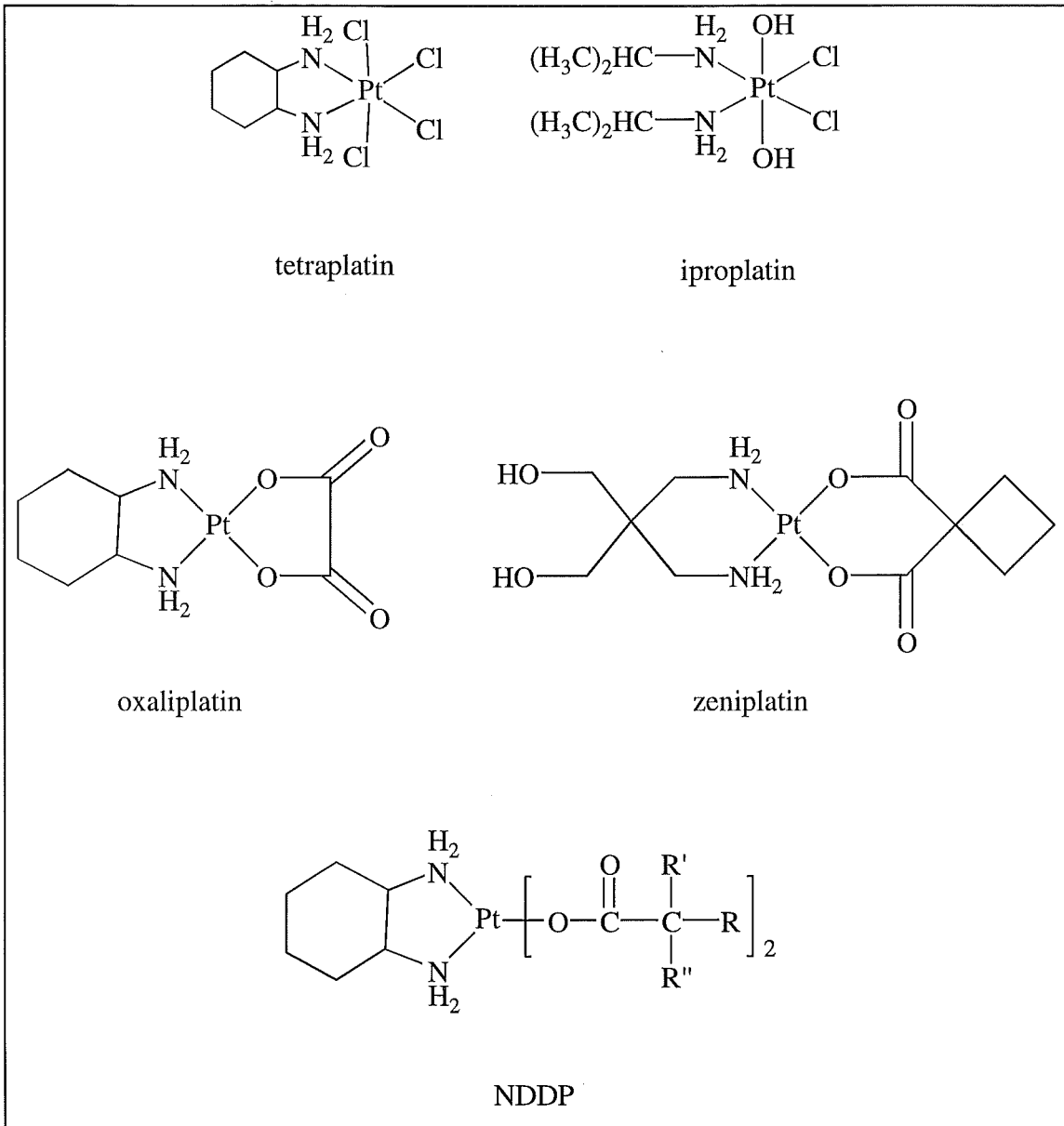


Figure 1.2: Platinum anti-cancer drug analogues.

Oxaliplatin was first synthesised in 1978 and has an oxygen-containing

leaving group in the form of oxalate, while the other coordination sites contain 1,2-chxn. Although active in many murine tumours including cisplatin-resistant lines, this drug causes severe emesis and neurological problems. Some patients experienced acute paralysis of the extremities and lips beginning during the treatment and continuing for several days. Severe nausea was experienced by 50 % of those treated. Symptoms regressed over a six-month period with no permanent neurological damage. It has now been registered for use as a chemotherapeutic agent in France [35] with positive results.

It was thought that these chxn complexes would overtake cisplatin as perfect candidates for new improved drugs overcoming the cross-resistance problem with cisplatin and carboplatin. However, Phase I and II clinical trials have shown that chemical instability, poor solubility and high toxicity limited their clinical potential.

An alternative approach in using these compounds has been to entrap them in liposomes [36] eg. L-NDDP (liposome-entrapped *cis*-bis-neodecanato-*trans*-R,R-1,2-diaminocyclohexane platinum(II)). Entrapment lowers toxicity by reducing the bioavailability of the platinum drug and thus allowing use of complexes containing the non-cross-resistant chxn group [21]. It can also facilitate the use of drugs with poor solubility such as the above cyclohexanediamines. However, continuing drug instability and poor entrapment efficiency has hampered development.

The second category of analogues was based on carboplatin. It was thought that the oxygen-containing leaving group would provide both good water solubility and stability. Zeniplatin was more active than cisplatin but showed cross-resistance to many cell lines. It also gave rise to severe emesis, neurotoxicity and nephrotoxicity, with one patient dying of acute renal failure. Enloplatin gave a similar spectrum of effects to zeniplatin. These are not favourable and therefore no

therapeutic advantage is found over cisplatin and carboplatin.

Another cisplatin analogue entered into clinical trials was iproplatin (CHIP, JM-9) (Figure 1.2) [21, 30] (*cis, trans, cis*-$[Pt^{IV}Cl_2(OH)_2(C_3H_7NH_2)_2]$) which has the platinum in the +IV oxidation state. Randomised clinical trials showed that compared to carboplatin it offers no advantages in terms of either reduced toxicity or improved activity. It was not active in tumours that displayed resistance to cisplatin and carboplatin and it caused more severe gastrointestinal and haematological toxicity.

Most of the platinum drug discovery initiatives focused on circumventing cisplatin resistance. Research showed that there were no other drugs offering improvements over cisplatin and carboplatin. Work therefore began to identify a platinum complex that would produce a different array of adducts on DNA, thereby overcoming the problem of resistance. It was also noted that an orally active drug would be clinically advantageous with no hospitalisation required. This is important for the psychological well-being of the patient and also reduces financial costs. The third generation platinum complexes were developed to improve upon these ideas [31, 36].

JM-216 (bisacetatoamminedichlorocyclohexylamineplatinum(IV)) (Figure 1.1) [21, 37] entered clinical trials in 1992. It shows activity in cell lines resistant to cisplatin and carboplatin with a substantial amount being absorbed after oral administration. The toxicity of this complex is mainly limited to delayed-onset vomiting and minimal thrombocytopenia. No nephrotoxicity or neurotoxicity have been seen. This drug has the platinum in oxidation state +IV and in a similar fashion to other platinum(IV) drugs [38], it will probably be reduced *in vivo* to produce the corresponding platinum(II) complex.

Despite the lack of success in finding a new improved platinum anti-cancer drug, research is continuing to find a non-toxic drug that is orally active and non-cross resistant with cisplatin.

1.4 RESISTANCE TO CISPLATIN

Although the discovery of cisplatin was serendipitous, drug resistance is now proving to be a major impediment to the clinical success of the drug. Resistance may either be intrinsic (present at the onset of treatment) or acquired during successive treatments after an initial response to the drug. The quest to overcome this resistance, whether inherent or induced, has become the basis for a large proportion of research into platinum drug therapy [39 - 41].

There are three possible mechanisms for cellular resistance. The first is reduced drug accumulation in the cell. The mechanism for the transport of cisplatin into the cell is not well understood but it is most likely to be a combination of passive diffusion across the cell membrane and an energy-dependent gated channel. This may include Ca^{2+}-dependent protein kinase activity, cyclic AMP-dependent activity and Na^+, K^+-ATPase activity. The Na^+, K^+-ATPase inhibitor ouabain reduces accumulation of cisplatin in cells which can induce resistance to cisplatin. This also indicates that Na^+, K^+-ATPase plays a role in the delivery of cisplatin from the plasma into the cell. Any modifications of these mechanisms or changes in the cell membrane may result in reduced drug influx.

A second resistance mechanism involves induction of increased cellular levels of GSH (γ-glutamyl-cysteinyl-glycine). This reacts chemically with cisplatin via the free thiol group. It may either (i) form an inactive conjugate; (ii) react with Pt-DNA mono-adducts to prevent cross-linking to adjacent purines; or (iii) assist

enzymes that repair cisplatin-induced DNA damage. Metallothionein is a family of cysteine-rich proteins that bind strongly to heavy metals. It binds to cisplatin both intra- and extracellularly and can scavenge cisplatin even more efficiently than GSH. High levels of metallothionein have been observed in testicular tumours that are resistant to cisplatin [41].

A third possibility is an increase in the cellular capacity to repair or remove cisplatin-DNA adducts. This may be induced by platinum exposure, with patients on long courses of cisplatin treatment developing resistance to the drug. Several preliminary studies investigating tumour tissue have supported the theory that an increase in DNA repair is the key feature of cisplatin resistance [36]. Patients treated with cisplatin had an inverse relationship between clinical response and levels of repair in the leukocytes [36]. This means that the higher the response to the drug the lower the level of repair. Another experiment showed a three-fold increase in DNA repair following failed treatment with cisplatin when compared to the repair level before treatment [36].

It is now known that HMG-domain proteins can recognise DNA structural elements such as the bends in cisplatin-modified DNA. Models have been proposed to explain the association of the proteins with cisplatin-resistant DNA. Two of these models propose that they influence the repair of cisplatin-DNA adducts [42]. The 'damage-recognition' model suggests that the HMG-domain proteins bind to DNA adducts and serve as recognition elements for repair complexes. However, the 'repair-shielding' mechanism proposes that the HMG proteins bind tightly to the platinum-DNA adducts and prevent the repair complex getting to the place of damage on the DNA strand. Present evidence points toward this latter explanation being correct, as a desensitisation of cells to cisplatin was observed when the gene

encoding the HMG-domain protein IXR1 was interrupted [42].

By whatever mechanism cells become resistant to cisplatin it is a major problem, as previously responsive tumours are now unable to be treated. This means that researchers must find an alternative platinum based-drug that operates in a different manner to cisplatin.

1.5 THE HYDROLYSIS KINETICS OF CISPLATIN

In the earliest biological experiments with cisplatin it was noted that there was an initial insensitivity to the drug lasting about two hours. It was suggested that cisplatin was converted, over time, to the actual 'active' form of the drug. Studies on the aqueous chemistry of cisplatin can help to explain this phenonomen. In aqueous solution the labile chloride ligands are displaced in a step-wise manner by water molecules as shown in equations (1.1) and (1.2).

$$cis\text{-}[PtCl_2(NH_3)_2] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} cis\text{-}[PtCl(NH_3)_2(OH_2)]^+ + Cl^- \quad (1.1)$$

$$cis\text{-}[PtCl(NH_3)_2(OH_2)]^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} cis\text{-}[Pt(NH_3)_2(OH_2)_2]^{2+} + Cl^- \quad (1.2)$$

In addition to these two solvolyses there are many other hydrolysis reactions that may occur.

$$cis\text{-}[PtCl_2(NH_3)_2] + OH^- \xrightarrow{k_{OH}^{11}} cis\text{-}[PtCl(OH)(NH_3)_2] + Cl^- \quad (1.3)$$

$$cis\text{-}[PtCl(OH)(NH_3)_2] + OH^- \xrightarrow{k_{OH}^{12}} cis\text{-}[Pt(OH)_2(NH_3)_2] + Cl^- \quad (1.4)$$

$$cis\text{-}[PtCl(OH)(NH_3)_2] + H_2O \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} cis\text{-}[Pt(OH)(OH_2)(NH_3)_2]^+ + Cl^- \quad (1.5)$$

$$cis\text{-}[PtCl(OH_2)(NH_3)_2]^+ \rightleftharpoons cis\text{-}[PtCl(OH)(NH_3)_2] + H^+ \quad pKa=6.85 \quad (1.6)$$

$$cis\text{-}[Pt(OH_2)_2(NH_3)_2]^{2+} \rightleftharpoons cis\text{-}[Pt(OH_2)(OH)(NH_3)_2]^+ + H^+ \quad pKa=5.93 \quad (1.7)$$

$$cis\text{-}[Pt(OH_2)(OH)(NH_3)_2]^+ \rightleftharpoons cis\text{-}[Pt(OH)_2(NH_3)_2] + H^+ \quad pKa=7.87 \quad (1.8)$$

At equilibrium the relative amounts of all these platinum species vary as a function of the chloride ion concentration and pH.

In blood plasma the high chloride ion concentration (104 mM) stabilises cisplatin as the dichloro complex. After entering the cell by an unknown mechanism (thought to be a combination of passive diffusion and a gated channel) cisplatin can hydrolyse due to the low (4 mM) chloride ion concentration.

The reactive species *in vivo* are thought to be those containing a coordinated water molecule such as *cis*-$[PtCl(OH_2)(NH_3)_2]^+$. In contrast to coordinated chloride and hydroxide, water is easily substituted by other molecules. Inert hydroxo species may be formed (Equations (1.3) - (1.8)) and at very high concentrations these can dimerise and trimerise [43] however, this is generally considered unlikely under biological conditions.

As water is a much better leaving group than either chloride or hydroxide, the chloroaqua species will be the most likely reactive form of cisplatin *in vivo* and so hydrolysis will be the rate-limiting step in the reaction of cisplatin with biomolecules such as DNA. Miller and House *et al* [44 - 51] have accurately determined the kinetic parameters for most of the hydrolysis reactions ((1.1) - (1.5)) and concluded that the acid hydrolysis of cisplatin *in vivo* is unlikely to proceed beyond *cis*-$[PtCl(OH_2)(NH_3)_2]^+$. ^{195}Pt NMR work by Bancroft *et al* also suggests that *cis*-$[PtCl(OH_2)(NH_3)_2]^+$ is the predominant complex that reacts with biomolecules [52].

As well as the work of Miller and House [44 - 51], the rate of hydrolysis of platinum(II) complexes has been studied numerous times [25, 52 - 71] by many different workers and the results are summarised in reference [44]. Knowledge of the fundamental reaction chemistry of cisplatin and other platinum(II) complexes in solution can provide important information for the design of new platinum drugs.

1.6 MODELS FOR THE INTERACTION OF CISPLATIN WITH DNA

It is generally agreed that the anti-tumour activity of cisplatin arises from the ability of its hydrolysis products to bind to DNA and thus inhibit cell replication.

Each DNA strand has a backbone consisting of repeating deoxyribose phosphadiester units attached through the sugar moiety to the N9 atoms of the purine bases adenine (A) and guanine (G) or the N7 atoms of the pyrimidines cytosine (C) and thymine (T). The ordering of the bases from 5' to 3' on the DNA strand defines the sequence of that strand. Complementary strands of DNA are stabilised by hydrogen bonds between guanine and cytosine (G-C) and between adenine and thymine (A-T), called 'Watson-Crick' base pairs. The complementary strands are aligned in anti-parallel fashion to form a double helix which is also stabilised by stacking interactions between the parallel bases. The DNA double helix offers an electrostatic potential that attracts the positively charged platinum hydrolysis products thought to be responsible for the anti-tumour activity [43]. DNA has a large range of potential binding sites for platinum(II) due to its size and chemical complexity. Platinum(II) behaves as a 'class B' (soft) metal and so can form stable compounds preferentially with S (but also with N) donor atoms thus will react with N atoms of the DNA nucleobases. Metal binding to a nucleobase (such as guanine) can be affected by a variety of factors including basicity of the donor, steric effects, interligand interactions and the charge on the metal.

Coordination of these platinum species to DNA takes place in two steps. The first involves the formation of a monofunctional adduct, mainly at the N7 position of a guanine or adenine residue. The monofunctional adducts react further, mostly at the N7 of nearby guanines and to a smaller extent adenine, forming bifunctional adducts. If the coordinated nucleobases are on the same strand of DNA an

intrastrand cross-link is formed; if on different strands an interstrand cross-link forms. Platinum has also been shown to link DNA and proteins [72].

It is now generally accepted that the moderately labile monoaqua platinum species produced *in vivo* binds via an intrastrand cross-link to the N7 position on two guanine nucleobases. The first evidence for the interaction of cisplatin with DNA came from Rosenberg's early work when he observed filamentous growth in *E. coli*, that is inhibition of cell division but not cell growth [5]. Biochemical studies measuring the uptake of radiolabelled precursors for proteins and nucleic acids in human AV_3 cells *in vitro* and in Ehrlich ascites cells *in vivo*, showed inhibition of DNA synthesis with hardly any effect on RNA or protein synthesis [72]. Further evidence that cisplatin interacts with DNA is that DNA repair-deficient cells are more sensitive to cisplatin than DNA repair-proficient cell lines. A prophage induction study showed that biologically active platinum complexes induce lysis in lysogenic bacteria and that there is a good correlation between anti-tumour activity and prophage induction [73 - 74].

After the initial hydrolysis (see Section 1.5), binding of the cisplatin hydrolysis product to DNA occurs as follows [43]:

- Bifunctional binding to the N7 position of two adjacent guanine bases on one DNA strand ie. an intrastrand cross-link. This is the most prevalent binding mode and is responsible for ~ 60 % of the binding of cisplatin to DNA.
- Bifunctional binding to an adenine and a guanine on the same strand (~25 %).
- Bifunctional binding to two guanines on two different strands - an interstrand cross link (10 %).
- Monofunctional binding to a single guanine base (2 - 3 %).

- Bifunctional binding to two guanines separated by a third nucleobase.
- DNA-protein cross-linking (< 1 %).

The two major adducts formed by cisplatin are *cis*-[$Pt(NH_3)_2${d(pGpG)}] and *cis*-[$Pt(NH_3)_2${d(pApG)}]. These adducts are responsible for the inhibition of cell division. The *cis*-[$Pt(NH_3)_2${d(pGpG)}] adduct is very stable and only strong nucleophiles such as cyanide or thiourea can break the DNA-Pt bond. One of the many possible explanations for the large stability of the Pt-GN7 bond may be due to the intrinsic basicity of the G-N7 and an additional stabilisation through hydrogen bond interactions with G-O6 [74].

There have been many crystallographic and NMR studies on the interaction of cisplatin with various single (ss) and double (ds) stranded oligonucleotides in order to model the events that occur when cisplatin binds to DNA [43, 72, 75 - 79]. In ss DNA chains with AG and GG adducts, the two bases are coordinated through N7 in a 'head to head' orientation. The interaction with the 5'-phosphate group in the GG chelated DNA seems to be important as it is involved in a hydrogen bond with an NH_3 ligand of the platinum complex. This could account for the observation that active platinum drugs of this type require an acidic N-H group [73]. The phosphate-ammonia interaction may well induce and/or stabilise DNA distortions thereby interfering with the replication process.

Upon binding to cisplatin the double helix of the oligonucleotides is distorted to a kinked structure. Changes in the UV and CD spectra reflect a loss in normal base stacking within the helix. The melting temperature of DNA decreases and increasing amounts of cisplatin can unwind the double helical structure [74]. Gel electrophoresis has shown that the reaction of cisplatin with DNA results in a 35°

bend in the double helix at the intrastrand GG-N7N7 cross-link [74]. This altered structure may influence the protein-DNA interactions with DNA polymerases being blocked by the adducts formed by cisplatin and thus interfering with the replication process and inhibiting cell division [74].

Recently Lippard *et al* [75, 80] have determined the first X-ray structure of duplex DNA containing the major adduct of cisplatin (Figure 1.3). The structure shows that when cisplatin binds to adjacent guanine residues on the duplex DNA it severely distorts the double helix by causing a bend toward the major groove and a widening and flattening of the minor groove. The overall structure of the double helix remains intact and most of the distortion is absorbed by conformational changes in the sugar-phosphate backbone ie. the phosphate groups on the backbone move closer together at the site of the platinum binding. This structure reveals that DNA is a flexible molecule as it can accommodate an intrastrand cross-link by adopting an unusual structural conformation.

Stereochemical differences in the adducts formed by *cis*- and *trans*-platinum complexes imply that the anti-tumour activity is due to the formation of a specific structural motif on DNA which can trigger a cellular response leading to cell death. To investigate this, attempts have been made to identify cellular proteins that recognise cisplatin-DNA interactions with the ultimate goal of understanding how such an interaction may lead to the selective toxicity of the drug to tumour cells.

South Western Blot analyses have revealed the existence of two classes of proteins that recognise cisplatin-damaged DNA. One of these has been identified as HMG1 (high mobility group). This protein recognises d(GpG) and d(ApG) 1,2-intrastrand cross-links which comprise 85 % of the cisplatin adducts *in vivo*.

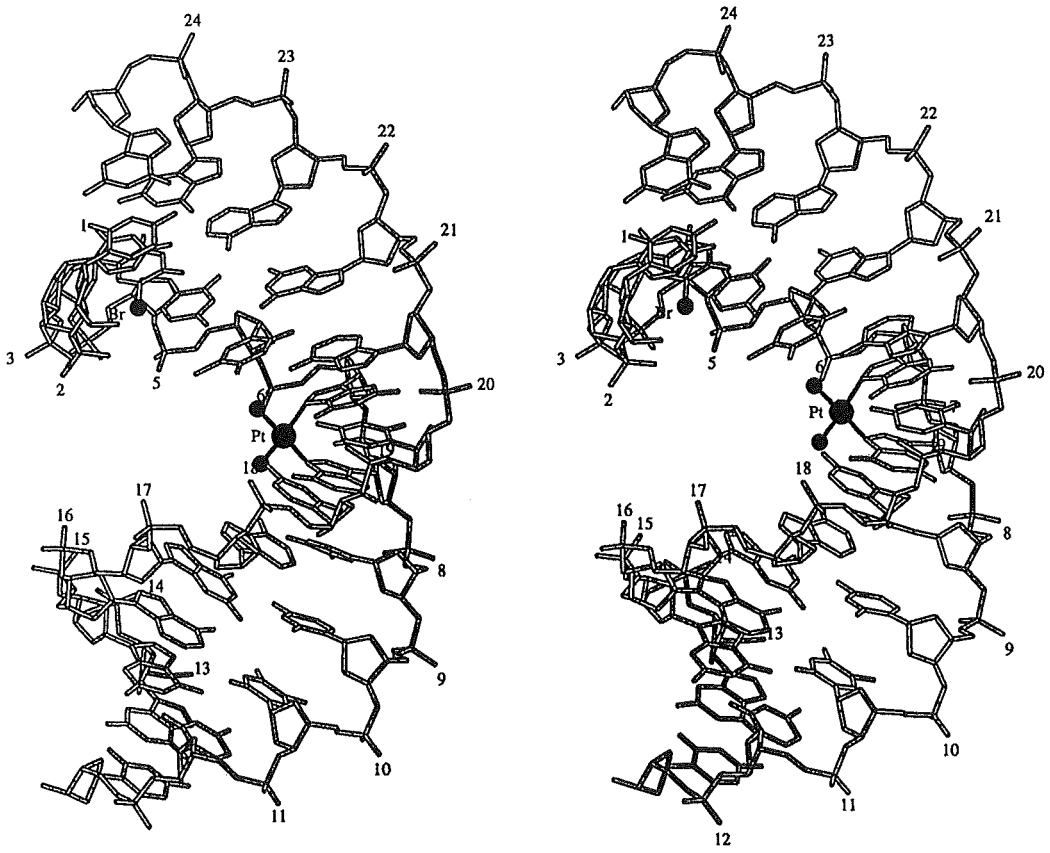


Figure 1.3: Stereoview of a ball and stick model of the duplex DNA, d(CCU^{Br}CTG*G*TCTCC).(GGAGACCAGAGG), where -G*G*- is modified by *cis*-{Pt-$(NH_3)_2$}$^{2+}$ [80].

These adducts bend the helix by 34° in the direction of the major groove and unwind it by 13° providing a signal for HMG1 binding. Other inactive platinum complexes unwind DNA to different degrees and these are not recognised by HMG1. Thus the degree to which DNA is unwound is an important determinant for HMG1 binding. HMG1 binds more strongly to DNA damaged by cisplatin than to unplatinated B-form DNA or to DNA modified with therapeutically inactive platinum analogues. The biological role of HMG1 is not known at present. Binding of it to platinum-modified DNA may prevent recognition of the adducts by cellular repair mechanisms. It is interesting to note that other investigators have observed lower levels of a protein of similar size to HMG1 found in cisplatin-resistant cell

lines [81]. Alternatively HMG1 may be required for active transcript in rapidly dividing cells and therefore removal of it by reaction with platinum drugs may cause cell death [81].

Another feature of cisplatin-DNA interactions is the speculative proposal that the platinum drug may be able to move along the DNA backbone. One model presented [82] is that the reaction of the drug with guanine is random but that the subsequent evolution of Pt-DNA cross-links may result in the breaking of the initial complexes, ie. the drug can 'walk' along the helix or 'jump' across helices. This effect has not been observed in ss DNA suggesting that it is not possible for the drug to jump over to another helix but in ds DNA it may walk down a helix by a mechanism that is dependent on the tertiary structure of the double helix.

During a physico-chemical study of cross-link modified DNA, Perez, Leng and Malinge [83] noticed that interstrand cross-links were not stable. Subsequent experiments showed that under physiological conditions, the bonds between platinum and N7 of guanine residues at the d(GC/GC) site are cleaved leading to the formation of monofunctional adducts. These can react further to form bifunctional intrastrand cross-links within the double-stranded DNA. This may account for the observation that more intrastrand cross-links are seen than are theoretically predicted.

In the thirty years since the discovery of the anti-tumour activity of cisplatin it is still not decisively known how the drug operates *in vivo*. However, with the use of X-ray studies and other techniques the picture is now becoming much clearer and hopefully within the next few years, the definitive pattern will emerge.

1.7 REDOX REACTIONS OF PLATINUM(II) AND PLATINUM(IV)

1.7.1 Reduction

Renewed interest into the redox chemistry of platinum(II)/(IV) began with the discovery of drugs such as JM-216 [21] where the platinum is in the +IV oxidation state. These drugs were developed in the search for an orally active complex as the toxicity of platinum(II) complexes limited their use to high hydration therapy. The derivatives prepared were either of the form *cis*-$[PtCl_4(am)_2]$ or *cis, trans, cis*-$[PtCl_2(OH)_2(am)_2]$. The hydroxo derivatives, synthesised by the oxidation of the corresponding platinum(II) complex with hydrogen peroxide, are generally more soluble than the tetrachloro derivatives.

Most evidence suggests that platinum(IV) complexes undergo ligand exchange processes very slowly and must be activated by reduction to the platinum(II) product prior to reaction with DNA [84 - 86]. Only those platinum(IV) complexes with active reduction products are biologically active. Thiol containing biomolecules such as cysteine and ascorbic acid appear to be the most likely intracellular reducing agents. Research by Pendyala *et al* [87] has shown that iproplatin (Figure 1.2) is partially converted to the platinum(II) complex *trans*-$[PtCl_2(NH_2CH(CH_3)_2)_2]$ (ie. a reduction product) in the blood and urine of patients receiving the drug. Eastman [38] showed that the reaction between tetraplatin and DNA requires the presence of glutathione *in vitro* and he postulated that the tetraplatin is activated *in vivo* by glutathione or other intracellular reducing agents. Gibbons [34] studied the rapid reduction of tetraplatin in tissue culture medium and found that the tetraplatin was reduced to $PtCl_2$(chxn) with a half life of 5 to 15 minutes depending on the level of protein sulfhydryl in the medium. However, a second explanation for the anti-tumour activity of platinum(IV) complexes may lie in

the observation that the complex *trans*, *cis*, *cis*-$[Pt(OH)_2Cl_2(NH_2Pr^i)_2]$ (CHIP, JM-9) can cleave DNA. Mong *et al* showed that the incubation of PM2 DNA with CHIP results in the formation of intrastrand cross-links and the appearance of DNA breakage. They speculated that, similar to bleomycin, the compound can produce hydroxyl or superoxide radicals which can cleave DNA.

Recent work on the reduction of platinum(IV) complexes comes from Elding *et al* [89]. They demonstrated that their model compound *trans*-$[Pt^{IV}Cl_2(CN)_4]^{2-}$ is rapidly reduced by thioglycolic acid, L-cysteine, DL-penicillamine and glutathione and that the thiolate anions are the most reactive species at physiological pH. This implies that reduction of platinum(IV) anti-tumour drugs by thiol-containing molecules may occur before interaction with DNA. They did similar work using L-methionine as the reducing agent [90]. The less reactive thioether-containing amino acid was able to be studied over a much broader pH range. In contrast to glutathione, there was only a small change in reaction rate within the pH range 0 - 12. Elding *et al* concluded that in neutral solution methionine-containing biomolecules will only compete for the reduction of platinum(IV) species when in the presence of low thiol concentrations. However, in acidic solution both species will be equally competitive.

Other very recent work involves the reduction of platinum(IV) by ascorbic acid [91]. Bose and Weaver proposed that ascorbate reductions proceed through a platinum(IV)-ascorbate intermediate whose formation is catalysed by platinum(II). They commented that the reactions were complex and difficult to interpret. This is in agreement with the more recent work of House [92] who was able to cleanly study the ascorbic acid reduction of a range of platinum(IV) complexes. They found standard first-order kinetics were followed when all solutions were oxygen free and EDTA was added to the solution to prevent interference from trace metal ions.

Ascorbic acid reduction has earlier been studied by Evans and Green [93] and Mehrotra *et al* [94]. The latter workers found a non-linear dependence on ascorbic acid which was attributed to the formation of an outer-sphere encounter complex prior to electron transfer. Similar effects were found by Sen Gupta *et al* when using hydroxylamine as a reducing agent [95].

Sen Gutpa *et al* also studied the reduction of platinum(IV) by sulfite [96]. They found the reaction to be a two-electron transfer which they confirmed by the lack of polymerisation of acrylamide when added to the reaction mixture. If radicals were present then it was expected that polymerisation would be observed.

Reedijk *et al* found that *trans, trans, trans*-$[Pt(NH_3)(C_6H_{11}NH_2)Cl_2(OH)_2]$ would only react with 5'-GMP, a biomolecule, in the presence of glutathione. A major product from this reaction was the reduced *trans*-platinum(II) complex [97]. Chandayot studied the base-promoted reduction of platinum(IV) and the reduction of *trans*-$[PtX_2(CN)_4]^{2-}$ by inorganic anions including SCN^-, CN^-, SO_3^{2-} in aqueous solution [98 - 99].

Peloso has published a large amount of work in the area of platinum redox kinetics. He has used such reductants as iodide [100- 101], Fe(II) [100 - 101] and platinum(II) [100 - 102] to reduce a range of platinum(IV) complexes. This has been used to investigate aspects such as ligand size (hence steric hindrance) on the rates of reduction. In most cases he found the reactions to obey second- or third-order rate laws and the reactions were sensitive to steric hindrance and σ-donor ability.

Moodley and Nicol [103] studied the reduction of platinum(IV) by Sn(II) and Cu(I). In the case of Sn(II) they found the reaction to proceed via one two-electron transfer step but for Cu(I) a non-complementary one-electron transfer occured

involving the formation of platinum(III) as an intermediate.

Sykes *et al* reported kinetic data for the platinum(IV) reduction by V^{2+} and $[Ru(NH_3)_6]^{2+}$ [104]. These reactions also involve the formation of platinum(III) as a transient intermediate and were found to occur via an outer-sphere mechanism.

The reduction of platinum(IV) can proceed by two pathways; one two-electron transfer step or two one-electron transfer steps [105]. Complimentary reduction reactions (one two-electron transfer step) involving platinum(IV) are the most well documented. Reactions belonging to this type of reduction usually occur via an inner-sphere transfer process where a bridged intermediate is formed between the two reactants prior to electron transfer. One such two-electron reductant is platinum(II) and thus it is possible to get reversible platinum(II)/platinum(IV) reactions. Non-complimentary processes are also known to occur and involve two one-electron transfer steps. This will result in the formation of platinum(III) which is an unstable oxidation state of platinum and produces short-lived intermediate species. These reaction types (complementary and non-complementary) also apply to the oxidation reactions discussed below.

1.7.2 Oxidation

The oxidation of platinum(II) is the most common route for the synthesis of platinum(IV) complexes. This is usually effected using hydrogen peroxide as an oxidising agent. Dunham *et al* used NMR and X-ray crystallographic techniques to study the oxidation of platinum(II) complexes by hydrogen peroxide. They found that the products produced were the *trans*-dihydroxyplatinum(IV) species, where the H_2O_2 added into one of the two vacant coordination sites and a water from solution adding into the other [106 - 107]. Harrigan and Johnson monitored the kinetics of the H_2O_2 oxidation of $[Pt(en)_2]^{2+}$ and $[Pt(NH_3)_4]^{2+}$ and found that the reactions

occurred by one two-electron transfer step [105]. They also studied the oxidation of these same complexes by peroxydisulfate and found the reaction occurred via two one-electron transfer steps. Drougge and Elding followed the oxidation of $[Pt(CN)_4]^{2-}$ by chlorine and hypochlorous acid using stopped-flow spectrometry [108]. Halpern and Pribanic [109] postulated the intermediate formation of Pt(III) in the oxidation of Pt(II) complexes by hexachloroiridate indicating two one-electron transfer steps. Peloso has also investigated the oxidation of platinum(II) complexes by hexachloroiridate [110 - 111] and found the oxidation to be chloride dependent. He studied the kinetics of the oxidation of Pt(II) complexes by tetrachloroaurate [88, 112] and found the reactions to be third-order for *trans* complexes but more complex for *cis* isomers. He has also used platinum(IV) complexes as oxidising agents [113] to give a third-order rate law dependent on Pt(II), Pt(IV) and Cl^-. This has also been observed by Mason [114]. Mason used bromine as an oxidising agent [115] in a two-step process. The first step was rapid producing a bromoaqua complex and the second slower step produced the dibromo complex. Zemskov considered possible oxidation reaction mechanisms including that for the oxidation of Pt(II) by permanganate and cerium(IV) [116].

1.8 THE *TRANS* EFFECT IN PLATINUM(II) CHEMISTRY

The *trans* effect has been defined as 'the effect of a coordinated group upon the rate of substitution reactions of ligands diagonally opposite to it in a metal complex'. Considering a ligand L, that means the oppositely-placed group will be an important factor in determining the reaction chemistry of L.

The chemistry of platinum(II) complexes is full of examples of the role the *trans* effect plays in synthesis and reaction chemistry and the extensive research that

went into this field has provided qualitative information on the *trans*-directing influence of various ligands. The approximate order of decreasing *trans* effect is:

$$CN^- > I^- > Br^- > Cl^- > NH_3 \sim H_2O \sim OH^- \sim py$$

This is an empirical order and it is concerned only with the rates of competing reactions. Kinetically the effect can be very large with a factor of 10^6 (or more) often being the difference in rate between a good *trans* labilising ligand and a ligand low in the *trans* series. It is generally accepted that the strong *trans* directing influence of CN^- is associated with its π accepting character.

The *trans* effect can be useful when synthesising isomeric platinum(II) complexes. For example, the *cis* and *trans* isomers of $[PtCl_2(NO_2)(NH_3)]^-$ can be made by reversing the order of introduction of groups into $[PtCl_4]^{2-}$. It can also be used to determine which chloride ion will be hydrolysed first in complexes such as $[PtCl_3(NH_3)]^+$. Due to the stronger *trans* effect of Cl^- over NH_3 the chloride diagonally opposite to another chloride will hydrolyse first.

Therefore the *trans* effect plays a major role in the substitution chemistry of platinum(II) complexes and in the design of synthetic reaction schemes. One application of this is the difference in reactivity between cisplatin and transplatin as discussed in Section 1.9.

1.9 CISPLATIN *VERSUS* TRANSPLATIN

Much research has focussed on trying to discover the differences between the activity of cisplatin and transplatin [52, 117]. In the solid state, these complexes differ only in geometry, but as is the case for many drugs, only one isomer has the required effect. Without going into great detail, the main points of interest regarding

the two isomers will be summarised.

Both cisplatin and transplatin are thought to interact with DNA even though the effects are less pronounced for transplatin. When interacting with DNA cisplatin forms mainly intrastrand cross-links and these are thought to be the main interactions necessary for anti-tumour activity. On the other hand, transplatin is unable to form intrastrand cross-links due to geometrical constraints, but it does form interstrand cross-links and also cross-links between DNA and proteins. Cisplatin-DNA adducts lead to thermal destabilisation but transplatin-DNA links seem to be of greater variability and cause thermal stabilisation or destabilisation. For cross-links of the type purine-X-purine, the intervening base, X, seems to be important with regard to activity.

Higher doses of transplatin are required in living cells to bind an equal number of platinum atoms per nucleotide, but bifunctional DNA adducts of either isomer inhibit DNA replication to the same extent. This has been interpreted as each isomer having a different repair mechanism.

The water molecule in aquated transplatin is kinetically more reactive than that for cisplatin (ie. $k_{-1}^{cis} = 64.6 \times 10^{-4}\ M^{-1}s^{-1}$ [49], $k_{-1}^{trans} = 160 \times 10^{-4}\ M^{-1}s^{-1}$) in agreement with the *trans* effect series ($Cl^- > NH_3$). However, the reactivity can be 'tuned' [118] by introducing a sterically hindering non-leaving group which slows the reactivity by retarding the formation of the five-coordinate intermediate (see Chapter 2). Such ligands include pyridine, thiazole and quinoline. Also, if equal amounts of cisplatin and transplatin are taken, the amount of aquated product at equilibrium will be less for the *trans* isomer than for the *cis* isomer due to the difference in equilibrium constants for equation (1.1) ($pK_{Cl}^{cis} = 2.17$, $pK_{Cl}^{trans} = 2.92$, 25 °C, I = 1.0 M).

Transplatin is less water-soluble than cisplatin. This may be problematic when infusing the drug into the bloodstream, but, at physiological concentrations, this will not be of great concern.

Although transplatin shows biological activity, it is quite toxic and not as active as the *cis* isomer due to the different array of adducts it forms with DNA. It has been found that certain *trans* isomers do inhibit tumour growth but they tend to be very individual complexes that defy all previous structure-activity relationships [119].

1.10 INTRODUCTION TO THE CURRENT RESEARCH

The initial investigations presented here follow on from the work of Miller and House *et al* [44 - 51] studying the aquation and anation of platinum(II) amine complexes. They studied the aquation of cisplatin and the chloride ion anation of the monochloro (*cis*-$[PtCl(OH_2)(NH_3)_2]^+$) species (Equation (1.1)). This work aims to complete the chloride ion dependence by measuring the chloride ion anation of the diaqua (*cis*-$[Pt(OH_2)_2(NH_3)_2]^{2+}$) complex using UV/Vis spectrometry (Equation (1.2)) and by indirectly measuring the aquation (k_2) of the monochloro species by free chloride ion titration. A further extension was to study the bromide ion anation of both the bromoaqua and diaqua platinum(II) complexes and to measure the effect of pressure on reaction rates for a selection of chloride and bromide anation reactions.

In light of the newer analogues of cisplatin containing platinum in the +IV oxidation state, it was decided to study the reduction of platinum(IV) complexes with a range of biological and abiological reducing agents. Ascorbic acid was selected as

it is thought to be one of the most likely *in vivo* reducing agents. Other reductants (Sn(II), Fe(II), $S_2O_3^{2-}$, hydroxylamine) were chosen because of their chemical significance in an effort to elucidate the underlying redox mechanisms. The preparation of these platinum(IV) complexes usually involves the oxidation of platinum(II) by hydrogen peroxide. Very little work has been done on the kinetics and mechanisms of the oxidation process so it was felt worthwhile to investigate the kinetics of platinum(II) oxidation.

In comparison with the lability of platinum(II), platinum(IV) is very inert to substitution and thus little has been done in way of kinetic studies, with complexes in this oxidation state. A starting point for investigating the chemical reactivity of d^6 platinum(IV) chloroammines is base hydrolysis, and work on this reaction is presented here.

This thesis therefore describes investigations of the solution chemistry of the anti-cancer drug cisplatin, various platinum(II) amines and their hydrolysis products, as well as some redox reactions of platinum(II)/(IV) complexes and the base hydrolysis of some platinum(IV) ammine complexes.

CHAPTER 2
EXPERIMENTAL

2.1 INTRODUCTION

The work in this thesis measures the rates of reaction for various platinum complexes undergoing a range of reactions. The main technique used for these measurements was UV/Vis spectroscopy, coupled with a high-pressure stopped-flow technique for certain reactions. ^{195}Pt NMR spectroscopy has been used for some product characterisation and X-ray crystallography was used to determine the structures of three platinum complexes synthesised during the course of this research.

This chapter gives a brief introduction of the techniques used, with more detailed information given in subsequent chapters.

2.2 UV/VIS SPECTROSCOPY

Conventional mixing spectroscopy (for reactions complete in greater than 10 minutes) and stopped-flow spectroscopy (reactions complete in under 5 minutes) were used to collect the data presented in this thesis.

2.2.1 Conventional mixing spectroscopy

The majority of data were obtained using the conventional mixing technique with a Perkin Elmer λ-2 Recording Spectrometer (Figure 2.1).

The general technique involved mixing two temperature equilibrated solutions (each containing a different reactant) or dissolving a small amount of solid

(~ 1 mg) in a solution at the appropriate temperature.

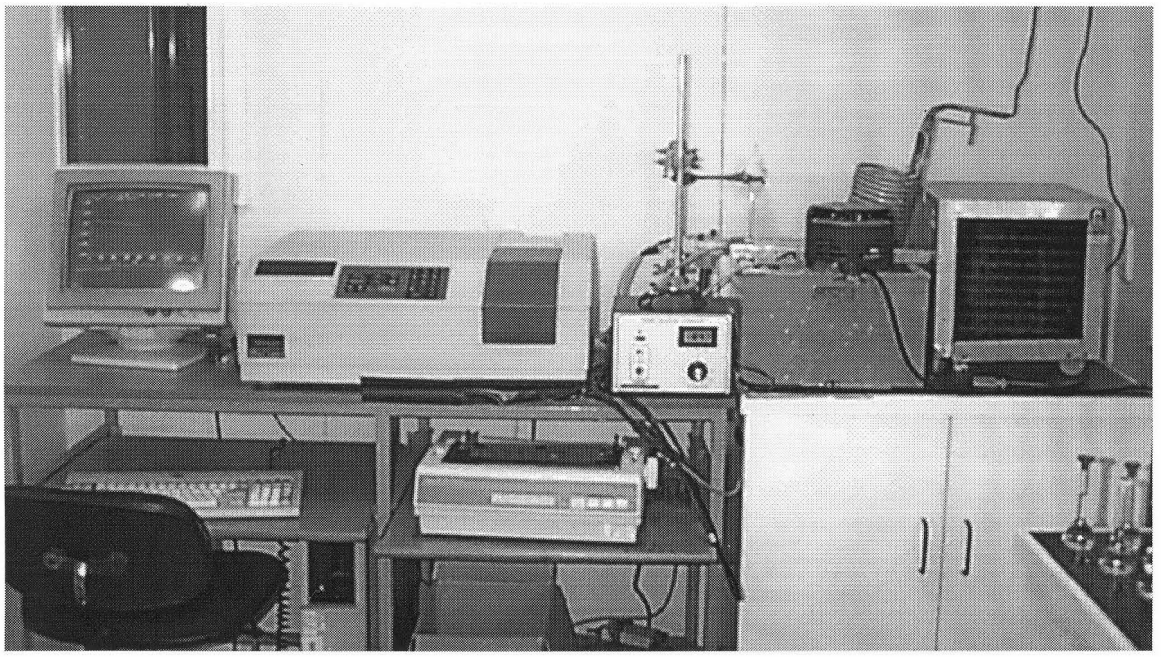


Figure 2.1: The Perkin Elmer λ-2 Spectrophotometer.

All solutions were thermally equilibrated in a water bath prior to reaction. Once mixed (or dissolved) the resulting solution was transferred by syringe to a cell in either an electrically heated cell-holder or to a water-cooled jacketed cell system. Solution temperature in the electrically heated cell was maintained using a thermostat, and the accuracy of the temperature gauge was confirmed using a Fluke 52 K/J platinum-resistance digital thermometer. For this experimental configuration, a 4 cm pathlength cell was used. For the water-cooled system, a small pump continually circulated water from the thermostatted bath through a water-jacketed cell (5 cm pathlength). The change in temperature during the 'dead-time', when the water passes from the bath to the cell, was not significant (< 0.1 °C). This configuration was used for reactions being studied at temperatures $10 \leq T \leq 30$ °C.

Measurements at temperatures below 10 °C were not possible due to fogging of the cell window. The electrically heated cell-holder was used for higher temperatures ($30 \leq T \leq 60$ °C).

2.2.2 Stopped-flow spectroscopy

Stopped-flow apparatus was required for studying rapid reactions. Data were obtained using an Applied Photo-Physics SX-18MV Biosequential Reaction Analyser. Reactions studied on this equipment were performed at the University of Erlangen-Nürnberg. Reactants were prepared and placed in two syringes. These syringes were connected to the top of the stopped-flow apparatus and the contents used to fill the internal syringes (Figure 2.2).

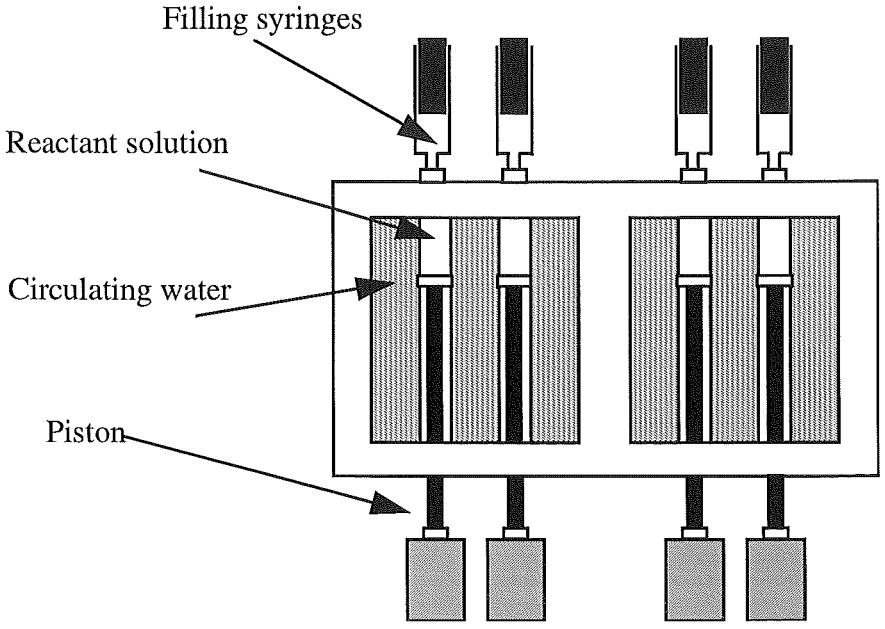


Figure 2.2: Representation of a stopped-flow apparatus.

A computer was used to set necessary parameters (eg. wavelength, scantime, timebase) before the reaction was started. Each reaction was measured 14 times and the rate constant evaluated using the Applied Photo-Physics software [120]. There were minimal differences between runs (± 2 %) and an average of the data collected was used in calculating the final rate constant.

2.2.3 Data collection

Where conventional mixing was used, absorption spectra of the individual reactants were initially run to determine if there was a 'window' in which to monitor any absorption changes (ie. an area where only one of the reactants absorbed). A repeat scan was then run. This involved measuring the complete absorption spectrum of the mixture (~ 200 nm to ~ 600 nm), at appropriate concentrations and time intervals to establish if there were any changes in absorption by which the reaction could be monitored. To successfully study a reaction this absorbance difference (ΔA) must be at least 0.1 absorbance unit. If there is sufficient change the reaction may then be studied at a fixed wavelength, following the decrease (or increase) in absorbance of either a reactant or product. Under pseudo-first-order conditions and from the final absorbance *versus* time scan, the observed rate constant can be calculated. Reactions were followed for 6 - 8 half lives (until constant absorbance was reached) and data were collected at various temperatures, allowing calculation of the activation parameters - activation enthalpy ($\Delta H^{\#}$) and activation entropy ($\Delta S^{\#}$).

2.3 HIGH-PRESSURE STOPPED-FLOW SPECTROSCOPY

High-pressure stopped-flow instrumentation was used to study selected kinetics of anation reactions at elevated pressure. The high-pressure stopped-flow instrument consisted of a cell block which is placed inside a water-jacketed pressurising vessel. This allowed constant temperature to be maintained via an external water reticulation system. The cell block (constructed out of teflon) was composed of two reactant syringes, a mixing/optical block and a receiver syringe (Figure 2.3). The reactants are placed in the syringes and mounted onto the block. The receiver syringe is fully depressed allowing the waste solution to flow into it. The entire block is then placed into the pressurising vessel and the system sealed. n-Heptane was used as the pressurising medium. A switch connected to the data collection system activated a step-motor (incorporated into the pressurising vessel). This motor depressed the two reactant syringes and a small portion of each reactant passed into the mixing chamber (a 'shot') and past the sapphire window.

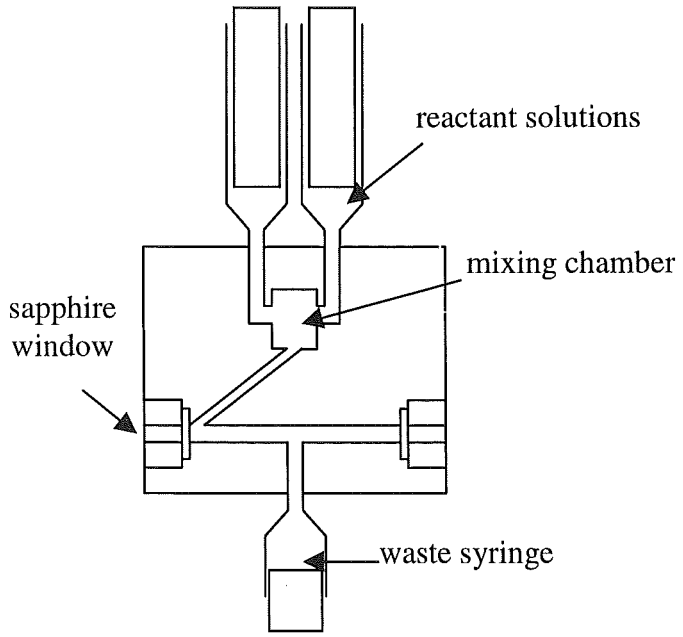


Figure 2.3: Schematic diagram of the high-pressure stopped-flow apparatus.

The reaction was monitored by UV/Vis spectroscopy. The reactant solution is then driven into the receiver syringe and the cycle repeated. Approximately twenty 'shots' can be used from one filling of the syringes.

As before, reactions were followed for 6 - 8 half-lives and pseudo-first-order ($[X^-] \geq 10[Pt(II)]$) rate constants evaluated using the KINFIT kinetic software package (On Line Instrument System (OLIS)). Mathematical manipulation (see 2.6.2) of the rate constant data allowed calculation of the activation volume ($\Delta V^{\#}$).

2.4 ^{195}Pt NMR SPECTROSCOPY

^{13}C and ^{1}H NMR spectroscopy have been widely used for structural identification of organic compounds for many years. More recently other nuclei (eg. ^{15}N , ^{19}F, ^{31}P, ^{195}Pt) have been used in structure determination. ^{195}Pt NMR was used in some of this work as an aid in identifying reaction products.

The ^{195}Pt NMR spectral data in this work were collected on a Unity XL300, referenced to $H_2[PtCl_6]$ (0 ppm). This instrument is not ideal due to the large (~ -3000 to ~ 3000 ppm) chemical shift range. It is necessary to do four individual scans to cover the entire spectral range and so it can be a time consuming process to find a peak. The low concentrations of platinum (10^{-3} M) exacerbated this problem as longer acquisition times were needed to have a sufficiently large signal to noise ratio.

2.5 X-RAY CRYSTALLOGRAPHY

Three X-ray structures are presented in this thesis. The data were collected on a Siemens P4 instrument and refined using a full matrix least-squares method on

F^2. There was no refinement of H-atoms. Full details of the structures and selected parameters are given in the relevant sections of this thesis (Table A3.6, Table A6.3). Crystallographers from the Chemistry Department X-Ray Laboratory performed the structural analyses.

2.6 NUMERICAL ANALYSIS

2.6.1 Calculation of rate constants and activation parameters

Within this work two types of reactions were observed; those following pseudo-zero-order kinetics and those following pseudo-first-order kinetics. The absorbance *vs* time spectra for zero-order reactions show a linear increase (or decrease) in absorbance before a sharp levelling off (Figure 2.4(A)). For this type of reaction the rate constant is simply the slope of the line. A first-order reaction produces an exponentially shaped plot (Figure 2.4(B)) (with exponential decrease also possible) and rate constants must be calculated (see equation (3.3), page 46).

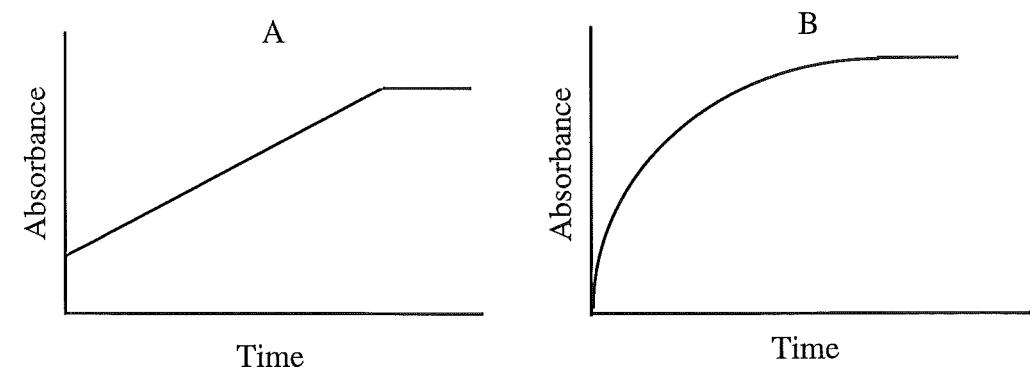


Figure 2.4: Schematic representations of absorbance *vs* time plots for (A) a zero-order reaction and (B) a first-order reaction.

About 30 data points (at fixed time intervals) are extracted from the absorbance *vs*

time output and entered into a computer programme specifically written for calculation of the rate constants ('SIAN'). The rate constants at a range of temperatures are then used to calculate the activation parameters $\Delta H^{\#}$, $\Delta S^{\#}$, and the rate constant at 25 °C using another specifically written programme 'EACT'. Errors for the calculation of rate constants are taken as ± one standard deviation. In all cases these errors are less than 5 %. Error parameters in $\Delta H^{\#}$ are calculated automatically by the computer programme using a linear least-squares analysis. Errors in $\Delta S^{\#}$ are assumed to be three times those for $\Delta H^{\#}$.

The variation of rate constant with temperature was first quantified by Arrhenius who proposed equation (2.1) [121]. This states that as the temperature increases, the reaction rate will also increase.

$$k = PZexp(-E_a/RT) \qquad (2.1)$$

In equation (2.1) k is a general rate constant, E_a is the activation energy, T is the absolute temperature, R is the gas constant, Z is the collision rate between reactant molecules and P is a probability factor inserted to allow for the disparity between calculated and observed values of k. The logarithmic form of this equation

$$\ln k = \ln PZ - E_a/RT \qquad (2.2)$$

when plotted as $\ln k$ *vs* 1/T is linear with a slope of $-E_a/R$ and a vertical intercept of lnPZ.

E_a and PZ can be determined directly if there is a range of known rate constants at known temperatures. Once determined they can be used to calculate the activation enthalpy ($\Delta H^{\#}$) and activation entropy ($\Delta S^{\#}$). If equation (2.2) is integrated between the limits $k = k_1$ at $T = T_1$ and $k = k_2$ at $T = T_2$ then

$$\ln(k_2/k_1) = E_a/R((T_2 - T_1)/T_1T_2) \quad (2.3)$$

and, if two values of k at two different temperatures are known E_a can be calculated. Alternatively when E_a and k (at one temperature) are known, k at a second temperature can be calculated. This second method is used (by the EACT programme) to calculate the rate constant at 25 °C.

An alternative approach to reaction kinetics is transition state theory [122]. This theory postulates that before undergoing a reaction an activated complex must form. The activated complex is in equilibrium with the reactants and the rate of reaction is controlled by the concentration of this complex present at any instant. The activated complex is assumed to have the properties of an ordinary molecule and to possess some inherent temporary stability. On the basis of these ideas,

$$k = (RT/Nh)\exp(-\Delta G^{\#}/RT) \quad (2.4)$$

where N is Avogadro's number, h is Planck's constant and $\Delta G^{\#}$ is the free energy of activation. Since the activated complex is in equilibrium with the reactants, standard thermodynamics can be applied giving

$$\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#} \quad (2.5)$$

and

$$k = (RT/Nh)\exp(\Delta S^{\#}/R)\exp(-\Delta H^{\#}/RT) \quad (2.6)$$

Since $\Delta H^{\#}$ can be related to activation energy ($\Delta H^{\#} = E_a - RT$) then

$$PZ = (RT/Nh)\exp(\Delta S^{\#}/R) \quad (2.7)$$

Thus from the determination of rate constants over a range of temperatures, the parameters E_a, lnPZ, $\Delta H^{\#}$, $\Delta S^{\#}$, and k (at a second temperature) can be calculated.

Activation entropy is a measure of the total entropy change taking place in the reactants and the solvent on the formation of the activated complex. Its sign and

magnitude are determined mainly by the charge of the activated complex relative to the charge of the reactants. For reactions between oppositely charged ions, the activated complex will have a lower charge than the reactants and thus will be less solvated (ie. less ordered). As formation of the activated complex is therefore accompanied by an increase in disorder, the activation entropy is positive. For a reaction between ions of like charge this theory predicts that $\Delta S^{\#}$ will be negative. Where one reactant is neutral and the other charged, $\Delta S^{\#}$ is predicted to be close to zero.

2.6.2 Theory behind activation volume

This section gives a simple derivation of the equation used to calculate activation volume from rate and pressure data, and a brief description of the theory behind the technique. A more complex derivation involving chemical potential may be found in Appendix 1.

$\Delta V^{\#}$ can be obtained from a plot of ln*k* *vs* P where the slope = $-\Delta V^{\#}/RT$. Three possibilities can arise:

(i) *k* increases with an increase in P giving a negative $\Delta V^{\#}$.

(ii) *k* decreases with an increase in P giving a positive $\Delta V^{\#}$.

(iii) *k* is independent of P (ie. no volume change from initial state, IS, to transition state, TS).

Now $\Delta V^{\#} = V_{TS} - V_{IS,}$ and if $\Delta V^{\#}$ is positive then the transition state is of larger volume than the initial state. Conversely if $\Delta V^{\#}$ is negative, the transition state is of smaller volume than the initial state.

One method to derive the expression 'slope = $-\Delta V^{\#}/RT$', considers the standard equilibrium reaction

$$X + Y \rightleftharpoons XY \qquad (2.8)$$

where $K = k_1/k_{-1}$ is the equilibrium constant for the reaction.

Standard thermodynamics gives

$$V = (-\partial G/\partial P)_T \quad (2.9)$$

so $$\Delta V = (-\partial \Delta G/\partial P)_T \quad (2.10)$$

and since $$\Delta G^{\#} = -RT\ln k \quad (2.11)$$

so $$(\partial \ln k/\partial P)_T = -\Delta V/RT \quad (2.12)$$

as required.

The most common unit of pressure used is MPa. In most cases experimental pressures ranged from 10 to 200 MPa. In aqueous solutions the extent of compression is 10 - 20 % and so the risk of explosion is negligible (note: 1 bar = 10^5 Pa = 0.1 MPa = 0.986 atm = 14.5 psi).

2.7 THE MECHANISTIC INTERPRETATION OF $\Delta S^{\#}$ AND $\Delta V^{\#}$

It is possible to propose certain reaction mechanisms for the substitution of square-planar complexes by considering the activation entropy ($\Delta S^{\#}$) and volume ($\Delta V^{\#}$) [123].

There are three main types of mechanism for ligand substitution reactions: associative, dissociative or interchange. A dissociative mechanism involves a step where an intermediate of reduced coordination number forms before being converted into the product. An associative mechanism involves a step where an intermediate of higher coordination number is formed. An interchange mechanism occurs in one step ie. the leaving and entering groups exchange in a single step by forming an activated complex, but not a true intermediate. This last mechanism is probably the most common pathway for substitution reactions of square-planar complexes.

Activation volume is a measure of the difference in molar volume between the reactants and the activated complex. Information about the volume change experienced by the complex and entering ligand is a good guide to the reaction mechanism. A small ($< 10\ cm^3mol^{-1}$) positive $\Delta V^{\#}$ indicates a dissociative-interchange reaction and in contrast, a small negative $\Delta V^{\#}$ points to an associative-interchange mechanism.

An important feature affecting the entropy of activation is the effect of a change in charge that occurs when an activated complex forms. If two ions of like charge form the activated complex (ie. charge density increases), the solvent molecules around the complex will become more ordered. This decreases the entropy and hence $\Delta S^{\#}$ is negative. If the reaction leads to a charge reduction in the activated complex (ie. two oppositely charged ions combine), the solvent molecules around the complex become more disordered and $\Delta S^{\#}$ is positive.

A large negative value of $\Delta S^{\#}$ points to an associative-interchange mechanism whilst a large positive entropy indicates a dissociative-interchange mechanism.

In their simplest forms, these interpretations predict that if a substitution process is observed to have both $\Delta V^{\#}$ and $\Delta S^{\#}$ negative then an associative-interchange mechanism is the most likely.

CHAPTER 3
HYDROLYSIS KINETICS OF PLATINUM(II)-AMINE COMPLEXES

3.1 INTRODUCTION

A knowledge of the reaction chemistry of cisplatin and other related complexes in aqueous solution is very important if the mode of action of cisplatin *in vivo* is to be understood. It is now agreed that in plasma, cisplatin remains in the dichloro form ($[PtCl_2(NH_3)_2]$) for the first few hours, due to the high chloride ion concentration. Once the drug is transported across the cell membrane (by a mechanism which is not yet fully understood) it can undergo hydrolysis reactions (eg. Equation (3.1)), due to the large drop in chloride ion concentration (104 mM to 4 mM). One product from these reactions is the chloroaqua species, $[PtCl(NH_3)_2(OH_2)]^+$, which is thought to be responsible for the anti-tumour activity of cisplatin. A further possible hydrolysis reaction may occur giving the diaqua product ($[Pt(NH_3)_2(OH_2)_2]^{2+}$) (Equation (3.2)). This species is easily generated in the laboratory and provides an entry into the chemistry of the chloroaqua complex, but is unlikely to exist in the biological situation [52].

While it is generally agreed that DNA is the primary target of cisplatin (or, more specifically, hydrolysis products of cisplatin), it is important to establish the simple kinetic and equilibrium properties of such complexes. Miller and House *et al* have recently [44 - 51] described a complete speciation profile for cisplatin in aqueous solution over a wide pH range and, along with others [124, 125] this information is being extended to further $[Pt(N)_2X_2]$ ($X = Cl^-, Br^-$) systems [49, 51].

A large quantity of work has studied the interaction of cisplatin (and its hydrolysis products) with DNA and other biomolecules. These molecules include simple amino acids, DNA substituents (ie. guanine, adenine, cytidine, histidine) and other molecules including 5'-GMP and purines [62, 126 - 143].

$$[PtX_2(NH_3)_2] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [PtX(OH_2)(NH_3)_2]^+ + X^- \qquad (3.1)$$

$$[PtX(OH_2)(NH_3)_2]^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} [Pt(OH_2)_2(NH_3)_2]^{2+} + X^- \qquad (3.2)$$

where $K_1 = k_1/k_{-1}$ and $K_2 = k_2/k_{-2}$ ($X^- = Cl^- / Br^-$).

It should be remembered that there are several other reactions involving the aqua/hydroxy equilibrium (See Chapter 1, Section 1.3), but under biological conditions, starting with $[PtCl_2(N)_2]$, the predominant species within the cell will be the chloroaqua/chlorohydroxo complexes in equilibrium [52].

In this chapter the kinetics and equilibria associated with reaction (3.2) for chloride ion anation are examined. These data complete the chloride dependent rate constant and equilibrium constant information associated with Scheme 3.1 (excepting K_3, see page 68) for $(N)_2$ =*cis*-$(py)_2$, en, chxn, tn, Me_2tn and *trans*-$(NH_3)_2$. Similar information is reported for the equivalent bromide ion anation reactions for the calculation of k_{-2}, k_1, k_{-1} and K_1 (Equations (3.1) and (3.2)). The effect of pressure on selected anation reactions is also discussed.

3.2 EXPERIMENTAL

3.2.1 Materials

The platinum(II) complexes were either commercially available (*cis*-$(NH_3)_2$, *cis*-$(py)_2$, *trans*-$(NH_3)_2$, chxn; Strem) or synthesised (en, tn, Me_2tn) as described by Miller *et al* [49]. The chloride (NaCl) and bromide (NaBr) ion solutions were prepared from AnalaR reagents (BDH). A background ionic strength of 1.0 M ($HClO_4$) was used for all standard kinetic experiments, while I = 0.1 M ($HClO_4$) was used for the high-pressure studies.

3.2.1.1 Chloride ion anation (k_{-2})

Solutions of $[Pt(OH)_2(N)_2]$ were generated by base hydrolysis of the corresponding dichloro complex [49]. For all complexes except *cis*-$(py)_2$, 50 mg of complex was dissolved in 50 mL 0.01 M NaOH and the solution heated on a steam bath for 3 - 5 hours before being left to cool overnight [49]. To simulate dark conditions the glassware was wrapped in aluminium foil. Concentrations of these solutions were: *cis*-$(NH_3)_2$ 3.33 mM, *trans*-$(NH_3)_2$ 3.33 mM, en 3.07 mM, tn 2.96 mM, chxn 2.63 mM and Me_2tn 2.73 mM. To confirm completeness of base hydrolysis, acidified solutions were titrated with standard Hg^{2+} solution. Diphenylcarbazone (phenylazoformic acid 2-phenylhydrazide), dissolved in isopropanol, was used as an indicator [144a]. The titrations gave Pt : free chloride ion ratios of 1:2.0 ± 0.2 in all cases indicating hydrolysis was complete. There was no evidence to suggest the formation of any polymeric μ-hydroxo platinum(II) species [45]. *Trans*-$[PtCl_2(NH_2)_2]$ (50 mg) required about 14 days in 50 mL 0.01 M NaOH at room temperature for complete hydrolysis, but complete chloride release was also achieved by heating the solution at 80 °C (steam bath) for 5 hours (in the

dark) followed by overnight cooling at room temperature. For the hydrolysis of *cis*-$(py)_2$, 5 mg was dissolved in 100 mL of 0.1 M NaOH ([*cis*-$(py)_2$] = 0.12 mM) and treated as above.

Upon acidification the dihydroxo complex is immediately converted to the diaqua species which, in the presence of halide ion, undergoes the two anation steps (Equations (3.1) and (3.2)). Because $k_{-2} \geq k_{-1}$ the two reactions can be followed separately at isosbestic points characteristic of the reaction not under study.

3.2.1.2 Bromide ion anation (k_1, k_{-1}, k_{-2})

The bromide ion anation of platinum(II) diaqua (k_{-2}) complexes was studied using stopped-flow techniques. In these cases the platinum(II) solutions were prepared as for chloride ion anation (see 3.2.1.1), but using 50 mg of complex dissolved in 100 mL 0.01 M NaOH. This resulted in concentrations of: *cis*-$(NH_3)_2$ 1.67 mM, *trans*-$(NH_3)_2$ 1.67 mM, en 1.53 mM, tn 1.48 mM, chxn 1.32 mM and Me_2tn 1.37 mM.

Platinum(II) solutions for the bromide ion anation of the bromoaqua and aquation of dibromo (k_{-1} and k_1) were prepared as for the chloride anation of the diaqua (ie. 50 mg of complex per 50 mL of solution). Concentrations of these solutions were: *cis*-$(NH_3)_2$ 3.33 mM, *trans*-$(NH_3)_2$ 3.33 mM, en 3.07 mM, tn 2.96 mM, chxn 2.63 mM and Me_2tn 2.73 mM.

3.2.2 Kinetics

In both the chloride ion anation of the diaqua and the bromide ion anation of the bromoaqua, aliquots (5 mL) of the base hydrolysed solutions (~3 mM in Pt(II) and 6 mM in Cl^-) were added to 5 mL of 2.0 M $HClO_4$ containing 30 - 80 mM

dissolved NaCl or NaBr, both at the appropriate temperature. These solutions were thermostatted in a water bath to ensure temperature equilibration prior to reaction. The newly acidic solution was quickly transferred to a temperature controlled spectrophotometer cell (4 or 5 cm pathlength) and the change in absorbance monitored at fixed wavelength using a λ-2 Perkin Elmer Recording Spectrophotometer. For the chloride anation of the diaqua the actual wavelengths used correspond to an isosbestic point for reaction (3.1) (*cis*-$(NH_3)_2$ 245 nm, *trans*-$(NH_3)_2$ 235 nm, en 283 nm, tn 270.2 nm, chxn 283 nm, Me_2tn 269.8 nm, py 230 nm) to minimise interference from this step.

The chloride ion anation reactions were followed for 6 - 8 half-lives and pseudo-first-order ($[Cl^-] \geq 10[Pt(II)]$) rate constants (k_{obs}) were calculated from the usual absorbance *vs* time expression (3.3).

$$k_{obs}t = \ln\{(A_\infty - A_0)/(A_\infty - A_t)\} \qquad (3.3)$$

Plots of k_{obs} *vs* $[Cl^-]$ were linear with slope = k_{-2} and zero intercept (within experimental error), indicating $k_2 < 5 \times 10^{-4}$ s^{-1} at 25 °C. Thus $k_{-2} = k_{obs}[Cl^-]^{-1}$, and the variation of k_{-2} with temperature allows the calculation of the activation parameters listed in Table 3.1. Full details of k_{obs}, $[Cl^-]$, temperature and k_{-2} are given in Table A3.1. The variation of k_{-2} with ionic strength (I) is given in Table A3.2.

Similar procedures were used for the bromide ion anation of the bromoaqua complex $[PtBr(N)_2(OH_2)]^+$. In this case, the rate of the first anation step (corresponding to the reverse of Equation (3.2)) was sufficiently rapid (Figure 3.1) as to be complete in the time of mixing (except for $(N)_2$ = *cis*-$(py)_2$). The rate of the second step (Equation (3.1), X^- = Br^-) was measured at an appropriate wavelength

(*cis*-$(NH_3)_2$ 260 nm, *trans*-$(NH_3)_2$ 335 nm, en 332 nm, tn 300 nm, chxn 243 nm, Me_2tn 300 nm, *cis*-$(py)_2$ 281 nm) corresponding to an isosbestic point for reaction (3.2). In these cases, plots of k_{obs} *vs* [Br^-] were linear with positive intercepts: the slope corresponding to k_{-1} ($M^{-1}s^{-1}$) and the intercept to k_1 (s^{-1}) ie. $k_{obs} = k_1 + k_{-1}$ [Br^-]. Activation parameters are listed in Tables 3.3 (k_{-1}) and 3.4 (k_1). Full details of k_{obs} (calculated using Equation (3.3)), [Br^-] and temperature are given in Table A3.3 and A3.4.

The bromide anation of the diaqua species, $[Pt(N)_2(OH_2)_2]^{2+}$, was measured using a Biosequential SX-18MV Stopped-Flow Reaction Analyser (Applied Photo-Physics). Reactions were again followed for 6 - 8 half-lives and the pseudo-first-order ([Br^-] ≥ 10[Pt(II)]) rate constants (k_{obs}) calculated by the Applied Photo-Physics software package [120]. The reactions were monitored at fixed wavelengths (*cis*-$(NH_3)_2$ 275 nm, *trans*-$(NH_3)_2$ 330 nm, en 290 nm, tn 280 nm, chxn 290 nm, Me_2tn 280 nm). Preliminary experiments to determine these wavelengths were performed on a Shimadzu UV-2101 PC UV/Vis Scanning Spectrometer. Plots of k_{obs} *vs* [Br^-] were linear with slope = k_{-2} and zero intercept (within experimental error). Raw data are presented in Table A3.5.

The variation of k_{-2} (Br^-) with temperature allows the calculation of the activation parameters $\Delta H^{\#}$ and $\Delta S^{\#}$ (Table 3.6).

3.2.3 Equilibrium constants for reaction (3.2)

Solutions of $[Pt(OH)_2(N)_2] + 2Cl^-$ (generated by base hydrolysis of the dichloro complex as described above), were acidified with $HClO_4$ and the systems allowed to reach equilibrium by heating for 4 hours at 80 °C in the dark followed by 24 hours at

25 °C. The free chloride ion concentration (T) was determined by Hg^{2+} titration [144a] and the equilibrium constant K_2 (Equation (3.2)) was calculated from the expression (3.4) (derived in Appendix 2) [156].

$$T^3 = K_1T(a - T) + K_1K_2(2a - T) \quad (3.4)$$

where $a = [Pt]_{initial}$ and K_1 ($= k_1/k_{-1}$) is the previously determined [49] equilibrium constant for Equation (3.1). Using the values for k_{-2} obtained, values for k_2 (Equation (3.2)) can be estimated from the expression $k_2 = k_{-2}K_2$. These data are listed in Table 3.4.

3.2.4 Synthesis of $[PtBr_4(N)_2]$ complexes

Residue solutions from the bromide ion anation of $[PtBr(N)_2(OH_2)]^+$ were allowed to evaporate at room temperature in open beakers. After several weeks orange crystals were deposited ($(N)_2$ = en, tn), which proved suitable for single crystal X-ray analysis. Similar orange platinum(IV) products were deposited for $(N)_2$ = chxn and Me_2tn, but these were unsuitable for X-ray analysis. ^{195}Pt NMR chemical shifts (relative to H_2PtCl_6) for $[PtBr_4(N)_2]$ dissolved in DMF are $(N)_2$ = en -1473 ppm, chxn -1431, tn -1307, Me_2tn -1364. Variations in δ_{Pt} are usually considered to be caused mainly by variations in the paramagnetic contribution to the shielding thus for a similar range of complexes such as these only a small variation in chemical shift is expected.

3.2.5 Crystal Structures

The single crystal X-ray structures of $[PtBr_4(en)]$ and $[PtBr_4(tn)]$ were determined on a Siemens P4 spectrometer using Mo radiation by Professor M.

Turnbull. Table A3.6 lists the crystal characteristics, X-ray data collection parameters, and solution and refinement procedures for [$PtBr_4$(en)] (I) and [$PtBr_4$(tn)] (II).

3.2.6 Effect of pressure on selected anation reactions

High-pressure stopped-flow instrumentation was used to study the kinetics at elevated pressure for some anation reactions in order to calculate the activation volume ($\Delta V^{\#}$). To calculate $\Delta V^{\#}$, the reactions must be studied with all variables except pressure, fixed ie. constant wavelength, concentration and ionic strength. All reactions were studied with a background ionic strength of 0.1 M ($HClO_4$).

Rate constants for the anation of the diaqua (k_{-2}) may be obtained under these conditions. $\Delta V^{\#}_{-2}$ can then be calculated from the slope of the $\ln k_{-2}$ *vs* P plots (as described in Chapter 2 of this thesis). For these reactions [X^-] (ie. concentration of anating ligand) was fixed at 0.05 M.

Both k_1 and k_{-1} (and hence $\Delta V^{\#}_{-1}$ and $\Delta V^{\#}_1$) can be calculated from the same experimental data but both the concentration (of anating ligand) and the pressure must be varied. To effect this, the reactions were studied at four concentrations (0.5, 0.75, 1.0, 1.25 M) and up to six pressures. Plots of $\ln k_{obs}$ *vs* [X^-] (where X = Cl^- or Br^-) were plotted for each pressure to give k_1 from the intercept and k_{-1} from the slope of these plots for each P. $\Delta V^{\#}$ was then obtained as above for both k_x (ie. $\Delta V^{\#}_{-1}$ and $\Delta V^{\#}_1$). Data for k_1 were not used (and hence $\Delta V^{\#}_1$ was not calculated) as the errors in determining the intercepts were too large.

3.3 RESULTS AND DISCUSSION

3.3.1 Chloride ion anation

The rates of chloride anation (k_{-2}, Equation (3.2)) for several $[Pt(N)_2(OH_2)_2]^{2+}$ complexes were measured in acidic solution over a 15 – 20 °C temperature range. The raw data are presented in Table A3.1. As expected for a reaction between ions of opposite sign, a negative salt effect is observed (Table A3.2) for $(N)_2$ = *cis*-$(NH_3)_2$, and an effect of similar magnitude is assumed for the other $(N)_2$ complexes.

The rate of anation of the *cis*-diaqua ions is 14 times greater than that of the monoaqua, (*cis*-$[PtCl(NH_3)_2(OH_2)]^+$, $k_{-1} = 6.46 \times 10^{-4}$ $M^{-1}s^{-1}$ [49] and $k_{-2} = 9.27 \times 10^{-2}$ $M^{-1}s^{-1}$), but this ratio increases to 94 for anation of *trans*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ relative to *trans*-$[PtCl(NH_3)_2(OH_2)]^+$ ($k_{-1} = 160 \times 10^{-4}$ $M^{-1}s^{-1}$ and $k_{-2} = 151 \times 10^{-2}$ $M^{-1}s^{-1}$) .

It should also be noted that the water molecules in both the *trans*-diaqua and *trans*-monoaqua are more labile than in the corresponding *cis* isomer, but the effect is more marked for the *trans*-diaqua. This is mainly due to a significant decrease in activation enthalpy associated with k_{-2} ($\Delta H^{\#}_{cis} = 66.3$ kJ mol^{-1}, $\Delta H^{\#}_{trans} = 50.6$ kJ mol^{-1}, Table 3.1).

The *trans* effect (Section 1.8) can be used to explain the difference in aquation and anation rates between transplatin and cisplatin. For aquation, the *trans* effect of Cl^- is greater than that of NH_3 and so substitution reactions will take place preferentially *trans* to Cl^-. Transplatin has both the chloride atoms *trans* to each other and thus hydrolysis (substitution of a Cl^- by H_2O) will occur at a faster rate than in cisplatin which has both chlorides *trans* to an NH_3 group. However, this is not observed in this work or in work by Miller *et al* [49]. With regard to anation, for

transplatin substitution *trans* to a chloride will be faster than the corresponding cisplatin anation where anation will be opposite an ammine ligand which has a less strong *trans* effect. This is the observed order (ie. *trans* > *cis*) for the anation process.

Table 3.1: Activation parameters for the first step in the chloride anation of some $[Pt(N)_2(OH_2)_2]^{2+}$ complexes (I = 1.0 M[a]).

$(N)_2$	$10^2 k_{-2}$ ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})
cis-$(NH_3)_2$	9.27 [b]	66 ± 2	-42 ± 6
	9.45 [c]	66 ± 4	-44 ± 12
	9.39 [d]	65± 2	-44 ± 6
	8.9 [e]	-	-
cis-$(py)_2$	20.0 [b]	72 ± 2	-17 ± 6
en	31 [f]	37 ± 12	-130 ± 36
	24.5 [b]	59 ± 1	-59 ± 3
R_1-en	32.2 [g]	67 ± 1	-28 ± 3
chxn	21.4 [b]	66 ± 2	-36 ± 6
	32.2 [h]	67 ± 1	-28 ± 3
tn	34.4 [b]	67 ± 3	-28 ± 9
Me_2tn	33.2 [b]	57 ± 3	-61 ± 9
trans-$(NH_3)_2$	151 [b]	50 ± 1	-72 ± 4

[a] See Table A3.1 for the effect of ionic strength on k_{-2}. [b] This research. [c] Recalculated from the data in Ref. [45]. [d] Data from this research and Ref. [45] combined. [e] Ref. [145], ionic strength not stated. [f] Ref. [124]. [g] R_1-en is a bicycloalkyl-substituted 1,2-diaminoethane ligand [124], I = 0.04 M. [h] Ref. [49] measured spectropolarmetrically.

Despite the fact that the *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ ion is at insignificantly low concentrations under biological conditions [46], anation reactions involving this species and biologically relevant nucleophiles have been widely investigated [69, 128, 133 – 135, 140, 146 - 155]. Some of these nucleophiles (eg. 5'GpG [151 - 152] or DNA [155]) react with *cis*-$[Pt(NH_3)_2(OH_2)]^{2+}$ up to 30 times faster than Cl^-, pointing to a very efficient platinum(II) capture process. This information is of prime importance when considering the biological interaction of cisplatin with DNA, as it is the binding of cisplatin to the mononucleotide guanine and to a lesser extent adenine, that disrupts the DNA helix. Competition with unproductive scavengers (ie. other biological nucleophiles) may lead to wastage of the drug as it can react with these components prior to reaction with the DNA in the tumour cells. It is these extraneous reactions that may be responsible for some of the side-effects caused by cisplatin chemotherapy.

The equilibrium constants K_2 (at 25 °C) associated with reaction (3.2), have been determined for various $(N)_2$. Using these values, together with k_{-2} data, estimates of k_2 have been obtained (Table 3.2). There have been very few direct k_2 measurements made [124], but the titrimetric method used here [156] gives estimates in good agreement with those obtained from a spectrophotometric procedure described previously [45]. The values obtained for k_2 are of the order of 10^{-5} s^{-1}, which are similar to those values for k_1 [49]. This indicates that the aquation processes of both the dichloro and monoaqua species are slow. The slow aquation time has been expressed as one of the reasons why cisplatin is the platinum(II) drug of preference. The change in chloride ion concentration across the cell membrane promotes formation of the chloroaqua species. The unfavourable equilibrium constant, K_2, for the second hydrolysis reaction means that formation of the diaqua is

unfavourable in the biological situation. The chloroaqua may react (in terms of ease/speed of reaction) with biological nucleophiles rather than aquate to the diaqua species. Other non-biologically active platinum(II) complexes have been shown to aquate at much faster rates and thus the inertness of cisplatin may be important in its clinical activity.

Table 3.2: Values of K_1, K_2, k_{-2}, k_2 estimated for the reaction between $[Pt(N)_2(OH_2)_2]^{2+}$ and Cl^- at 25 °C (I = 1.0 M).

$(N)_2$	$[Pt]_i$ (mM)	$[Cl^-]_{free}$ [a] (mM)	10^3K_1 [b]	10^4K_2 [c]	10^2k_{-2} ($M^{-1}s^{-1}$)	10^5k_2 (s^{-1})
cis-$(NH_3)_2$	1.67	1.595	6.42	2.94[d]	9.3	2.75[d]
en	0.767	0.742	1.50	3.21	25	8.0
chxn	0.658	0.569	1.81	3.98	21	2.2
tn	0.740	0.677	1.62	1.88	34	6.4
Me_2tn	0.683	0.643	3.22	2.85	33	2.7
trans-$(NH_3)_2$	0.833	0.600	1.19[e]	3.86	151	5.8

[a] Measured by $[Hg^{2+}]$ titration of an equilibrium solution. [b] I = 0.1 M [49]. [c] Calculated using equation (3.4). [d] Values of $K_2 = 2.7 \times 10^{-4}$ and $k_2 = 2.5 \times 10^{-5}$ s^{-1} have been previously estimated spectrophotometrically [49]. [e] This research.

This now completes information on the chloride-ion-dependent equilibria outlined in Scheme 3.1 (see page 68), (apart from K_3) for $(N)_2$ = *cis*-$(NH_3)_2$, en, chxn, tn, Me_2tn and *trans*-$(NH_3)_2$ and partial data for *cis*-$(py)_2$. Rate and equilibrium constants associated with Scheme 3.1 for other $(N)_2$ complexes are presented in Table 3.3.

Table 3.3: Rate and equilibrium constants (25 °C, I=0.1 M) associated with Scheme 3.1.

$(N)_2$	10^5k_1 (s^{-1})	10^3k_{-1} ($M^{-1}s^{-1}$)	pK_1	10^5k_2[a] (s^{-1})	10^2k_{-2}[a] ($M^{-1}s^{-1}$)	pK_2[a]
cis-$(NH_3)_2$[b]	4.15	6.46	2.17	2.75	9.27	3.53
trans-$(NH_3)_2$[c]	1.90	16.0	2.92	5.8	151	4.41
cis-$(py)_2$	5.87	9.42	2.20	-	20.0	-
en	3.20	21.1	2.82	8.0	24.5	3.49
R_1-en[d]	3.20	44.0	3.14	7.8	67.0	3.93
chxn	3.68	20.3	2.74	2.2	21.4	3.40
tn	5.88	36.1	2.79	6.4	34.4	3.73
Me_2tn	8.40	26.1	2.49	2.7	33.2	3.55

[a] I = 1.0 M. [b] $pK_a^1 = 5.93$, $pK_a^2 = 7.87$, $pK_a^3 = 6.85$ [157]. [c] $pK_a^1 = 4.24$, $pK_a^2 = 7.22$, $pK_a^3 = 5.63$ [157]. [d] Ref. [124].

There has been some controversy in the literature with regard to the rate of hydrolysis for the first step in the chloride release from *trans*-$(NH_3)_2$ relative to the *cis* isomer (k_1 in Equation (3.1)). Some estimates for k_1 (*trans*-$(NH_3)_2$) have been very indirect [158], but even the direct forward measurement is complicated by reversible first- and second-order kinetics [68]. The situation is made more difficult by the low aqueous solubility of transplatin. Arpalahti *et al* [158] found that k_1 *trans* > k_1 *cis* when studying the complexation of transplatin with inosine. As Miller and House [49] found the reverse it was decided to reinvestigate the reaction. Theory predicts that the stronger *trans* effect of Cl^- over NH_3 means *trans* > *cis* is the expected reaction order.

The procedures adopted previously [49] have been repeated here and the rate of

chloride ion anation of *trans*-$[PtCl(NH_3)_2(OH_2)]^+$ remeasured (using a wider $[Cl^-]$ range), where k_1 (intercept) and k_{-1} (slope) are directly obtained from plots of k_{obs} *vs* $[Cl^-]$ (Tables 3.4 and 3.5).

Satisfactory agreement for k_1 were obtained from the intercept (this work = 1.9 x 10^{-5} s^{-1}, [49] = 1.9 x 10^{-5} s^{-1} (25 °C)), but values for k_{-1} (this work = 160 x 10^{-4} M^{-1} s^{-1}, [49] = 305 x 10^{-4} M^{-1} s^{-1} (25 °C)) from the slope differ by a factor of almost two. This, in turn, changes the value for K_1 from 0.622 x 10^{-3} in [49] to 1.19 x 10^{-3} at 25 °C and our new estimate has been used in all subsequent calculations (Table 3.4) and throughout this thesis (eg. pages 28, 50). Despite the changes in the absolute value of k_{-1}, the activation parameters obtained for k_1 and k_{-1} in both investigations are comparable within experimental error (Table 3.8). Results from this work still indicate that the hydrolysis of cisplatin is greater than that for transplatin by a factor of 2.76. A similar trend is also observed for the analogous bromide anation studies where k_1 is calculated indirectly from the intercept of the k_{obs} *vs* $[Br^-]$ plots (*cis*/*trans* = 22.4). Why this ordering (*cis* > *trans*) goes against the *trans* effect and other studies [158] is not understood.

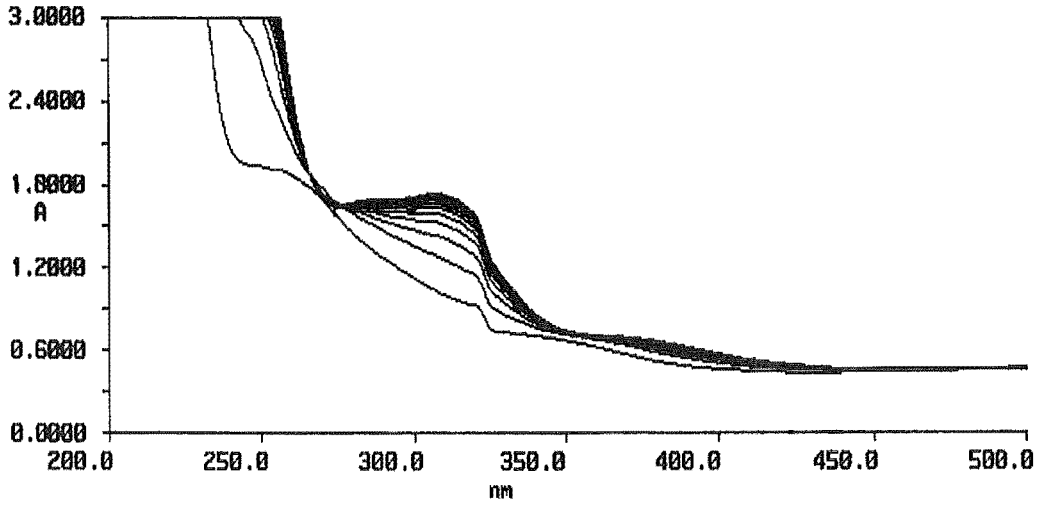
The *trans*-dibromo system gives a K_1 value about ten times greater than the analogous chloride system (K_1^{Br} = (15.2 x 10^{-4} /12.6 x 10^{-2}) = 12.1 x 10^{-3}) which appears to be a normal trend when $[PtBr_2(N)_2]$ systems are compared with $[PtCl_2(N)_2]$ (See Table 3.7).

3.3.2 Bromide ion anation

The reaction of bromide ion with $[Pt(N)_2(OH_2)_2]^{2+}$ is about five times faster than that of Cl^- but the rates were too rapid to measure using the conventional mixing

experimental conditions. These fast diaqua anation reactions were measured using stopped-flow techniques. It was possible however to measure the rate of the subsequent step (bromoaqua species, Equation (3.2)) once $[PtBr(N)_2(OH_2)]^+$ had been generated.

Figure 3.1: Repeat scans (180 s time interval) showing an increase in absorbance for the bromide ion anation of $(N)_2$ = tn.



The Br^- anation rate of the bromoaqua (k_{-1}) is again about 2 - 5 times greater than Cl^- anation with relatively constant $\Delta H^{\#}$ data within each series: $\Delta H^{\#} = 58 \pm 2$ kJ mol^{-1} for Br^- (Table 3.4) and $\Delta H^{\#} = 69 \pm 4$ kJ mol^{-1} for Cl^- [49], excluding the *trans*-$(NH_3)_2$ data.

Plots of k_{obs} *vs* $[Br^-]$ for reaction (3.2) were linear with positive intercepts and these were interpreted in terms of Equation (3.6)

$$k_{obs} = k_1 + k_{-1}[Br^-] \qquad (3.6)$$

with $K_1 = k_1/k_{-1}$.

Values for k_1, the rate of bromide release from $[PtBr_2(N)_2]$ at 25 °C, (Table 3.5)

are rather more dependent on $(N)_2$ than their chloro analogues [49] and the activation parameters are more variable but in general, the loss of the first bromo ligand from $[PtBr_2(N)_2]$ is about ten times faster than the loss of the first chloro ligand.

The *trans* effect theory can be used to partially explain why bromide ion anation is faster than chloride ion anation. Bromide has an even stronger *trans* effect than chloride and thus substitution is more favourable. It also has a greater overlap of the ligand orbital with the central platinum atom. It therefore implies that I^- reactions will be faster than Br^- reactions. This has been qualitatively confirmed by preliminary experiments which showed that the first anation step (k_{-2}) was not observable on the stopped-flow time scale while the second step was just observable using stopped-flow techniques.

Table 3.4: Activation parameters for the bromide anation of $[Pt\,Br(N)_2\,(OH_2)]^+$ (25 °C, I = 1.0 M $HClO_4$, $NaClO_4$, NaBr).

$(N)_2$	$10^2 k_{-1}$ ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})	$k_{-1}(Br)/k_{-1}(Cl)$
cis-$(NH_3)_2$	1.99	57.8 ± 2	-84 ± 6	3.08
cis-$(py)_2$	2.10	57.2 ± 3	-85 ± 9	2.23
en	6.40	63.5 ± 1	-55 ± 4	3.03
chxn	9.72	56.6 ± 4	-17 ± 10	4.79
tn	9.25	52.9 ± 1	-87 ± 3	2.56
Me_2tn	8.70	54.8 ± 1	-62 ± 3	3.33
trans-$(NH_3)_2$	12.6	69.0 ± 5	-31 ± 15	4.13
trans-$(NH_3)_2$[a]	1.60	78.1 ± 4	-17 ± 12	-

[a] Data for the Cl^- anation of *trans*-$[PtCl(N)_2(OH_2)]^+$ (I = 0.1 M).

The rates of bromide anation (k_{-2}, Equation (3.2)) for several $[Pt^{II}(N)_2(OH_2)_2]^{2+}$ complexes have been measured on the stopped-flow time scale in acidic solution over a 20 – 25 °C temperature range (raw data are presented in Table A3.5). Plots of k_{obs} *vs* [Br^-] were linear with zero intercept indicating $k_2^{Br} < 5 \times 10^{-5}$ s^{-1}. Comparison between the rate of anation (at 25 °C) for both chloride and bromide ions ($k_{-2}(Br^-)/ k_{-2}(Cl^-)$, Table 3.6) gives a constant ratio of 5.1 ± 0.4, excluding *trans*-$(NH_3)_2$ data. For *trans*-$(NH_3)_2$ this ratio drops to 2.8. This rate increase may be due to the larger orbital overlap for the bromide system.

Table 3.5: Activation parameters for the aquation of $[PtBr_2(N)_2]$[a] (25 °C, I = 1.0 M $HClO_4$, $NaClO_4$, NaBr).

$(N)_2$	$10^4 k_1$ (s^{-1})	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})	$k_1(Br^-)/ k_1(Cl^-)$
cis-$(NH_3)_2$	4.25	87.0 ± 2	-17 ± 6	8.1
cis-$(py)_2$	15.8	38.5 ± 2	-93 ± 6	27
en	5.12	70.0 ± 3	-73 ± 9	16
chxn	17.4	53.3 ± 1	-42 ± 3	47
tn	6.05	112 ± 5	+71 ± 15	10
Me_2tn	9.88	109 ± 4	+141 ± 12	12
trans-$(NH_3)_2$	15.2	45.7 ± 4	-69 ± 12	10
trans-$(NH_3)_2$[b]	0.19	83.1 ± 5	-17 ± 15	80

[a] These data were obtained from the intercept of k_{obs} *vs* [Br^-] plots. [b] Data for *trans*-$[Pt(N)_2Cl_2]$ (I = 0.1 M).

There is a relatively constant $\Delta H^{\#}$ within each series ($\Delta H^{\#}_{Br} = 68 \pm 2$ kJ mol^{-1},

$\Delta H^{\#}_{Cl} = 64 \pm 4$ kJ mol^{-1}) as was observed for the anation of the monoaqua (Table 3.4). For all complexes the activation entropy is negative, indicating an associative-interchange mechanism (as observed for the analogous chloride anation). The lability of the *cis*-diaqua ions is 10 - 20 times greater than that in the monoaqua ($[Pt^{II}X(N)_2(OH_2)]^+$), but this increases to 33 for the *trans*-$(NH_3)_2$ system (Table 3.6). As for the case of chloride anation, the *trans*-diaqua is more labile than the *cis* isomer due to a decrease in activation enthalpy ($\Delta H^{\#}_{cis} = 68$ kJmol^{-1}, $\Delta H^{\#}_{trans} = 56$ kJmol^{-1}).

Table 3.6: Activation parameters for the bromide anation of $[Pt(N)_2(OH_2)_2]^{2+}$ (25 °C, I = 1.0 M $HClO_4$).

$(N)_2$	k_{-2} ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})	$k_{-2}(Br^-)/k_{-2}(Cl^-)$	$k_{-2}(Br^-)/k_{-1}(Br^-)$
cis-$(NH_3)_2$	0.446	67.6 ± 1	-25 ± 3	4.81	22.4
en	1.29	70.9 ± 0.3	-5 ± 1	5.3	20.2
chxn	1.13	69.9 ± 1	-9 ± 3	5.3	11.6
tn	1.86	67.9 ± 1	-12 ± 3	5.6	20.1
Me_2tn	1.53	64.9 ± 1	-24 ± 3	4.6	17.6
trans-$(NH_3)_2$	4.23	56.4 ± 1	-44 ± 3	2.8	33.6

It is interesting to note that the order for the rate of reaction at 25 °C is the same (*trans* > tn > Me_2tn > en > chxn > *cis*) for both chloride ion and bromide ion anation of the diaqua although the spread is not large. We can suggest no reason for this order, other than unexplained steric factors. However note that for the diamines, a similar order has been observed for the aquation of *trans*-$[CoCl_2(N)_2]^+$ complexes [159].

The temperature variation of K_1 allows estimation of the quasi-thermodynamic parameters (non-standard state conditions) given in Table 3.7. Similar data are available for the chloride ion anation process [49] and the patterns based on the influence of $(N)_2$ are similar (within a large experimental error) for both anating ligands. All free energy data are positive, but there is variability within the activation enthalpy and activation entropy data.

Table 3.7: Quasi-thermodynamic parameters associated with the bromide anation of $[Pt\,Br(N)_2(OH_2)]^+$ (25 °C, I = 1.0 M).

$(N)_2$	$10^3K_1^{Br}$	ΔG^0_{-1} or $-\Delta G^0_{-1}$ (kJ mol^{-1})	ΔH^0_{-1} or $-\Delta H^0_{-1}$ (kJ mol^{-1})	ΔS^0_{-1} or $-\Delta S^0_{-1}$ (JK^{-1} mol^{-1})
cis-$(NH_3)_2$	21.3 (6.42)[a]	9.54	+29 ± 4	+65 ± 12
cis-$(py)_2$	75.2 (6.31)	6.41	-19 ± 5	-85 ± 15
en	8.0 (1.50)	12.0	+6.5 ± 4	-18 ± 12
chxn	17.9 (1.81)	9.97	-3.2 ± 4	-44 ± 12
tn	6.54 (1.62)	12.5	+59 ± 6	+156 ± 18
Me_2tn	11.3 (3.22)	11.1	+54 ± 5	+144 ± 15
trans-$(NH_3)_2$	12.1 (1.19[b])	10.9	-23 ± 9	-114 ± 27

[a] Values in parentheses are $10^3K_1^{Cl}$ data [49]. [b] This research.

3.3.3 Equilibrium relationships

If a platinum-containing compound is to be an effective anti-tumour agent then it is necessary for a reasonable concentration of the platinum-containing substitution-labile complex to be available at the site of the replicating tumour. Neither *cis*-$[PtCl_2(NH_3)_2]$ nor $[PtCl(OH)(NH_3)_2]$ are thought to react directly with DNA, but

both can provide a source of the 'active' $[PtCl(NH_3)_2(OH_2)]^+$. The amounts of these species present depends on the extent to which the equilibria represented by equation (3.7) occur ie. K_1 (= k_1/k_{-1}), and pK_a^3.

$$\begin{array}{l} cis\text{-}[PtCl_2(NH_3)_2] \underset{}{\overset{K_1}{\rightleftharpoons}} cis\text{-}[PtCl(OH_2)(NH_3)_2]^+ + Cl^- \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \Big\downarrow pK_a^3 \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad cis\text{-}[PtCl(OH)(NH_3)_2] \end{array} \qquad (3.7)$$

Considering this, it is interesting to see if variations of pK_a^3 or K_1 have been reported for the types of dichloroplatinum(II) that are either inactive or active in cancer chemotherapy.

The acid-base equilibrium constant K_a^3 is difficult to measure due to the competing anation of the chloroaqua by chloride ion during any potentiometric titration. It is only recently that values of pK_a^3 = 6.85 (25 °C) for cisplatin and pK_a^3 = 5.63 (25 °C) for transplatin have been determined [160 – 161]. It is also possible to estimate pK_a^3 as being equal to the pH at the half equivalence point when adding 1 mole of 1.0 M NaOH to a solution of the chloroaqua. This method gives a value of pK_a^3 = 7.25 at 45 °C (I = 0.2 M) [46]. For other complexes pK_a^3data are not available. Some workers have used the arithmetic mean of K_a^1 and K_a^2 (Scheme 3.1) as an estimate. The value for $[PtCl_2(en)]$ of 6.7 (estimated in this way) [162] does not differ greatly from that for cisplatin (6.85). In the absence of more precise measurements it has been assumed that values for all other $(N)_2$ complexes will be similar to 6.7.

A pK_a^3 value of 6.7 means that at physiological pH (7.4) a chloroaqua solution will contain about 78 % chlorohydroxo but with pK_a^3 = 5.63 (the transplatin value)

this proportion increases to 98 % [49]. Despite 78 % being a somewhat high percentage of inert chlorohydroxo it still remains an important source of active chloroaqua because, as the chloroaqua is removed from solution by complex formation, it will constantly be replaced from the 'store' of chlorohydroxo in proportions controlled by pK_a^3.

Consideration of K_1 values for cisplatin and transplatin (ie. 6.42×10^{-3} [49] and 1.19×10^{-3} , respectively) implies that there will be less of the chloroaqua species produced from transplatin than cisplatin. The unfavourable equilibrium concentration of *trans*-$[PtCl_2(NH_3)_2]$ (relative to cisplatin), and its much lower pK_a^3 value, prevent it from functioning as an effective anti-tumour drug under biological conditions. There is not enough *trans*-$[PtCl(NH_3)_2(OH_2)]^+$ available to effectively inhibit DNA replication. However, if sufficient chloroaqua can be produced from transplatin then it will be anti-tumour active. Values for other platinum(II) amine complexes (Table 3.2) all have lower K_1 values than cisplatin and using this rationale should be less effective anti-tumour agents. As none of these complexes have made it to clinical trials this may be an important point to consider when developing new anti-tumour drugs.

K_1 is the ratio of the forward (k_1, aquation) and reverse (k_{-1}, anation) rate constants of equation (3.1). The forward reaction, being between two neutral species, will proceed at a rate independent of ionic strength. The reverse reaction is however, a reaction between two singly charged species of the opposite sign. Because of this k_{-1} will decrease as the ionic strength increases. Consequently K_1 will also be ionic strength dependent with a value increasing with increasing I. Fortunately this dependence is not large, which means that the values of K_1 found by Miller [49] are probably satisfactory for the biological situation where the blood

plasma has an ionic strength of ~ 0.1 M.

It is interesting to compare the equilibrium constant K_1 for both chloride ion and bromide ion anation. K_1^{Br} is the larger value ($K_1^{Br} = 21.3 \times 10^{-3}$, $K_1^{Cl} = 6.42 \times 10^{-3}$) and this means that at equilibrium there will be more *cis*-$[PtBr(NH_3)_2(OH_2)]^+$ than *cis*-$[PtCl(NH_3)_2(OH_2)]^+$. For a 1 mM solution of the dihalo complex there will be 88 % of the *cis*-chloroaqua and 96 % of the *cis*-bromoaqua complex. This may lead to the speculative thought that *cis*-$[PtBr_2(NH_3)_2]$ may be a more effective anti-tumour drug than cisplatin as more of the anti-tumour active bromoaqua species is produced. However, the bromoaqua complex is more reactive than the equivalent chloride monoaqua and this may lead to it reacting indiscriminately with a wider range of nucleophiles and thus being less effective and causing more side-effects.

It has not been measured during the course of this work but it should be possible to measure the rate of chloride ion anation of the bromoaqua species. The main problem associated with this will be the production of the bromoaqua complex independent of diaqua and dibromo species. Likewise the bromide ion anation of the chloroaqua complex should also be possible. One method for generating pure chloroaqua using column chromatography has been previously described by Miller *et al* [44].

3.3.4 Crystal structures

In our work, it is general practice to retain the solutions from kinetic runs for platinum recycling after evaporation. Residues from the bromide ion anation studies were left in open beakers and after several weeks, small amounts of orange crystals deposited. These were assumed to be $[PtBr_2(N_2)]$, and so to confirm this assumption

a single crystal structural analysis was performed on the $(N)_2$ = ethylenediamine (en) compound. It was somewhat surprising to find that spontaneous oxidation had occurred and the products were platinum(IV) complexes $[PtBr_4(N_2)]$. This oxidation is thought to occur via atmospheric oxidation or through bromine oxidation (produced by atmospheric oxidation of bromide in the residue beakers). An X-ray structural analysis of the $(N)_2$ = propanediamine (tn) compound gave a similar result and the structures of neutral $[PtBr_4(en)]$ (I) and $[PtBr_4(tn)]$ (II) complexes are shown in Figure 3.2.

While the synthesis of $[PtCl_4(en)]$ has been reported [163], our work appears to be the first description of the tetrabromo complex. The average Pt(IV)-Br and Pt(IV)-N bond distances are 2.455(5) and 2.04(2) Å, respectively. The latter are very similar to Pt(II)-N distances (2.00 - 2.09 Å) in *cis*-$[PtCl_2(NH_3)_2]$ systems [47]. The five-membered ring torsion angle of 49.8° in $[PtBr_4(en)]$ indicates that the en ring is virtually strain-free [164].

3.3.5 Effect of pressure

A high-pressure stopped-flow instrument [165] was used to measure the activation volumes for some anation reactions of platinum(II) amine complexes. The reactions studied were chosen to fit within the limitations of the instrument (eg. wavelength).

In all systems studied (Table A3.7) it was found that k increases with P resulting in a small, negative $\Delta V^{\#}$ (-5 to -11 cm^3mol^{-1}) (Table 3.8). This indicates an associative-interchange mechanism which is in agreement with that indicated by the thermal activation parameters ($\Delta H^{\#}$ and $\Delta S^{\#}$) (Table 3.8). (See Chapter 2, Section 2.7).

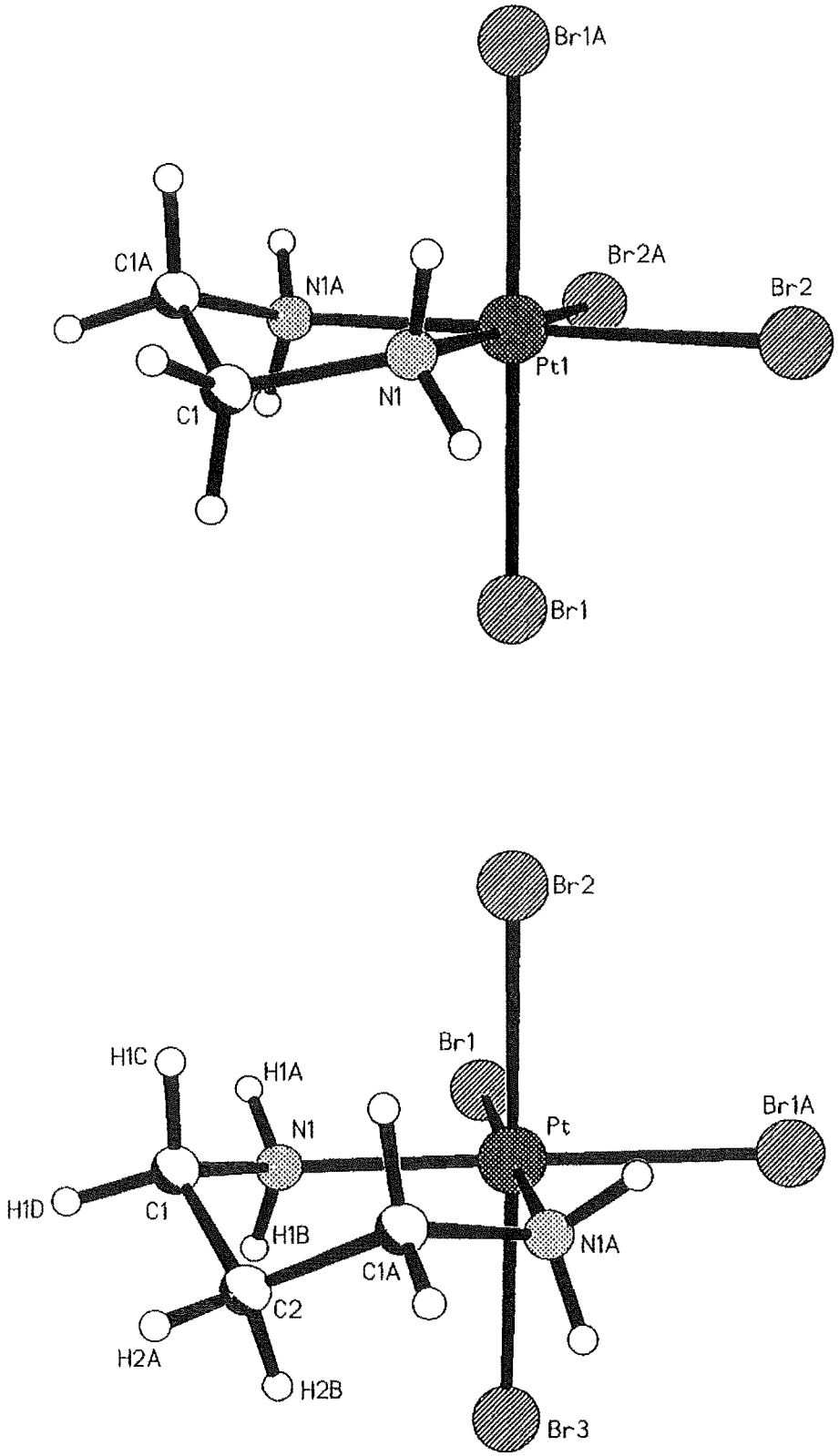


Figure 3.2: **X-ray crystal structures of $[PtBr_4(en)]$ (I) and $[PtBr_4(tn)]$ (II).**

There was very little difference in the values for the activation volumes for the chloride and bromide anation of both the diaqua (*cis*-$[Pt(N)_2(OH_2)_2]^{2+}$) and monoaqua (*cis*-$[PtX(N)_2(OH_2)]^{+}$) (Table 3.8). Activation volume values for the aquation of the platinum(II) complexes ($\Delta V^{\#}$) are not presented as it was found that the errors in determining the intercept of the appropriate plots were too large.

3.3.6 Comparison with palladium(II)

Platinum(II) and palladium(II) have comparable ionic radii (60 ppm and 64 ppm, respectively) and behave very similarly except for palladium(II) complexes being 10^5 more reactive than their platinum(II) analogues. This is mainly due to their kinetic lability and weaker Pd-X bond strengths. Both metals are soft Lewis acids and prefer N and S donor ligands. It is believed that high lability is one reason why palladium(II) complexes are ineffective anti-tumour agents. Although there is a large difference in reactivity between the two metals the overall equilibrium constants are similar and thus palladium(II) complexes can be used to model platinum(II) chemistry [166].

It was found that reported data for model palladium(II) complexes support the strong preference of platinum(II) drugs for the N7 position of guanine over other coordination sites of DNA [167]. There is also good correlation between the trends observed for palladium(II) and the analogous platinum(II) complexes, and therefore it is possible to extrapolate palladium(II) results to the biologically relevant platinum(II) situation. Excellent correlation between structure and reactivity are observed for the interaction of both metal centres with nucleic acid components [167].

3.4 CONCLUSIONS

The work presented in this chapter adds to the kinetic and equilibrium data available for the reaction of cisplatin and its derivatives with small nucleophiles. A complete list of data (rate, activation enthalpy, activation entropy and activation volume) are presented in Table 3.8. These activation parameters point towards the anation process occurring via an associative–interchange mechanism. This means that the reaction proceeds via the formation of a five coordinate transition state ie. both the entering group and leaving group are partially 'bound' to the central platinum atom and exchange by an interchange process. This is in agreement with other studies on the substitution of square-planar platinum(II) complexes, which have been found to proceed in this way.

The difference in reactivity across a range of platinum(II) amine complexes can be used to explain why cisplatin is the best (or most appropriate) anti-tumour active complex. Data for both the chloride and bromide anation/aquation show that cisplatin is the least reactive of all the complexes studied. This means that the drug is more likely to remain intact as the dichloro complex before reaching the tumour site. Side reactions between the chloroaqua species (produced by aquation) and other biological complexes (eg. thiols in proteins) are thus minimised and the *cis*-chloroaqua concentrations remain high, which therefore leads to a more effective chemotherapeutic drug.

Scheme 3.1: Rate and equilibrium constants for the hydrolysis of *trans*-$(NH_3)_2$ (I = 0.1 M, T = 25 °C).

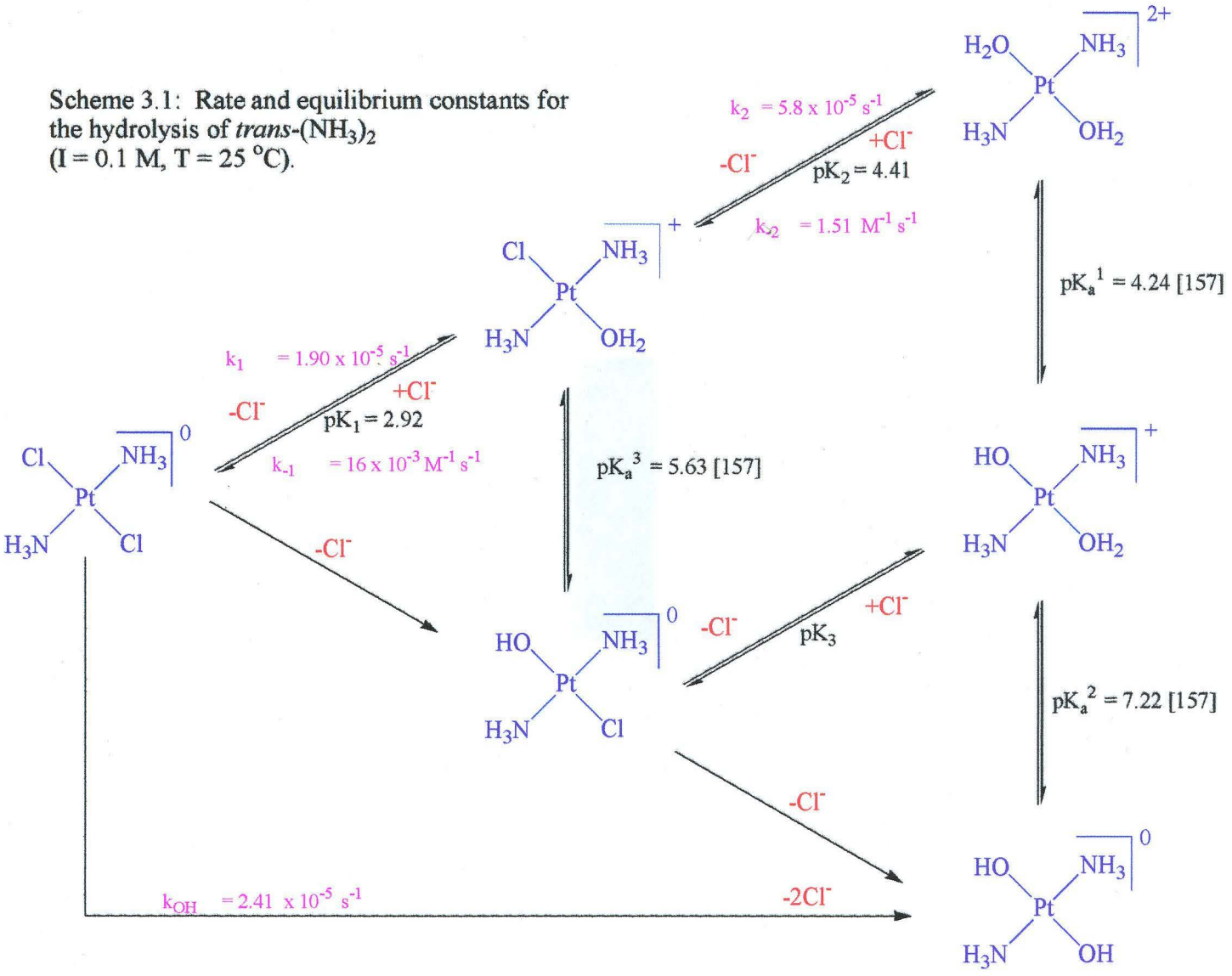


Table 3.8: Activation parameters for the aquation and anation of some $[PtX_2(N)_2]^{n+}$ complexes (1.0 M $HClO_4$).

	k_x[a]	$\Delta H^{\#}$ ($kJmol^{-1}$)	$\Delta S^{\#}$ ($JK^{-1}mol^{-1}$)	$\Delta V^{\#}$ (cm^3mol^{-1})	k_x[a]	$\Delta H^{\#}$ ($kJmol^{-1}$)	$\Delta S^{\#}$ ($JK^{-1}mol^{-1}$)	$\Delta V^{\#}$ (cm^3mol^{-1})	k_x[a]	$\Delta H^{\#}$ ($kJmol^{-1}$)	$\Delta S^{\#}$ ($JK^{-1}mol^{-1}$)	$\Delta V^{\#}$ (cm^3mol^{-1})
	X = Cl											
	cis-$(NH_3)_2$				*trans*-$(NH_3)_2$				en			
10^4k_{-1} ($M^{-1}s^{-1}$)	64.6[b]	76.9 ± 6[b]	-29 ± 12[b]	-	160[c]	78.1 ± 4[c]	-17 ± 12[c]	-	211[b]	69.7 ± 3[b]	-43 ± 6[b]	-9.4 ± 0.5[c]
10^5k_1 (s^{-1})	4.15[b]	93.6 ± 8[b]	-15 ± 16[b]	-9.5 ± 1.2[f]	1.60[c]	83.1 ± 5[c]	-17 ± 16[c]	-	3.2[b,c]	97.1 ± 3[b,c]	-5 ± 6[b,c]	-9.2 ± 1[f]
10^2k_{-2} ($M^{-1}s^{-1}$)	9.27[d,e]	66.3 ± 2[d]	-42 ± 6[d]	-	151[d]	50.6 ± 1[d]	-72 ± 3[d]	-	24.5[d]	58.8 ± 1[d]	-59 ± 2[d]	-5.27 ± 1[c]
	tn				Me_2tn				chxn			
10^4k_{-1} ($M^{-1}s^{-1}$)	361[b,c]	65.3 ± 2[b,c]	-53 ± 4[b,c]	-	261[b,c]	72.1 ± 6[b,c]	-33 ± 12[b,c]	-	203[b,c]	69.5 ± 5[b,c]	-44 ± 10[b,c]	-
10^5k_1 (s^{-1})	5.88[b]	97 ± 3[b]	-1 ± 6[b]	-	8.4[b,c]	82.6 ± 3[b,c]	-46 ± 6[b,c]	-	10.3[b]	55.2 ± 4[b]	-136 ± 8[b]	-
10^2k_{-2} ($M^{-1}s^{-1}$)	34.4[d]	67.2 ± 3[d]	-28 ± 9[d]	-7.41 ± 0.3[c]	33.2[d]	57.4 ± 3[d]	-61 ± 9[d]	-	21.4[d]	66 ± 2[d]	-36 ± 6[d]	-

	X = Br											
	cis-$(NH_3)_2$				*trans*-$(NH_3)_2$				en			
10^2k_{-1} ($M^{-1}s^{-1}$)	1.99[d]	57.8 ± 2.2[d]	-84 ± 7[d]	-10.2 ± 0.4[c]	12.6[d]	69.0 ± 5[d]	-31 ± 15[d]	-	6.4[d]	63.5 ± 1.2[d]	-55 ± 4[d]	-7.43 ± 0.3[c]
10^4k_1 (s^{-1})	4.25[d]	87 ± 2.3[d]	-17 ± 7[d]	-	15.2[d]	45.7 ± 4[d]	-69 ± 12[d]	-	5.12[d]	70 ± 3[d]	-73 ± 9[d]	-
k_{-2} ($M^{-1}s^{-1}$)	0.45	67.6 ± 0.7	-25 ± 2.1	-5.08 ± 0.6[c]	4.23	56.4 ± 1.3	-44 ± 3.9	-	1.29	70.9 ± 0.3	-5 ± 0.9	-5.7 ± 0.5[c]
	tn				Me_2tn				chxn			
10^2k_{-1} ($M^{-1}s^{-1}$)	9.25[d]	52.9 ± 1[d]	-87 ± 2[d]	-10.4 ± 0.8[c]	8.7[d]	54.8 ± 1[d]	-62 ± 3[d]	-	9.72[d]	56.6 ± 4[d]	-17 ± 10[d]	-
10^4k_1 (s^{-1})	6.05[d]	112 ± 5[d]	+71 ± 15[d]	-	9.88[d]	109 ± 4[d]	+141 ± 12[d]	-	17.4[d]	53.3 ± 1[d]	-42 ± 3[d]	-
k_{-2} ($M^{-1}s^{-1}$)	1.86	67.9 ± 0.7	-12 ± 2.1	-5.82 ± 1[c]	1.53	64.9 ± 1	-24 ± 3	-	1.13	69.9 ± 1	-9 ± 3	-

[a] See Equations (3.1) and (3.2). [b] Ref. [49]. [c] 0.1 M $HClO_4$. [d] Ref. [168]. [e] Ref. [45]. [f] Ref. [169].

CHAPTER 4

THE REDUCTION OF PLATINUM(IV) COMPLEXES

4.1 INTRODUCTION

One of the many early generalisations made regarding the structure-activity relationships of platinum anti-tumour agents was that the central metal must be in the +II oxidation state [23 – 26]. This is now known not to be a requirement for biological activity as there are currently platinum(IV) complexes which show particular promise as anti-tumour drugs. These include CHIP, *cis, cis, trans*-$[Pt^{IV}Cl_2(iPrNH_2)_2(OH)_2]$ [85, 93], tetraplatin, $[Pt^{IV}Cl_4(chxn)]$ [36, 21], oxaliplatin (Figure 1.2), a cyclohexanediamine containing complex [21], and JM-216, *cis*, *trans*, *cis*-$[Pt^{IV}Cl_2(OAc)_2(NH_3)$(cyclohexylamine)] (Figure 1.1) [21, 170]. These drugs are thought to act as prodrugs for platinum(II) species, with the active platinum(II) complexes being produced by reduction within the plasma. Studies have shown that when platinum(IV) drugs are administered to patients, the main excreted complex is the platinum(II) reduction product [34].

Such results raise the question as to the nature of the oxidation state of platinum when the drug finally reaches the site of the replicating cancer cells [21, 85], as platinum(IV) complexes are generally regarded as being substitutionally inert. Biological reduction of platinum(IV) to platinum(II) has been proposed [21], but further information on the rates of reduction of platinum(IV) species with both biological and abiological reducing agents is desirable. Recent information in this

area comes from the work of Peloso who used Fe(II) [171], ferrocene [100 - 101], iodide ion [100 - 101, 171] and platinum(II) complexes [100 - 102, 172] as reducing agents and Elding who used glutathione, R-(+)-(L)-cysteine, penicillamine, L-methionine and thioglycolic acid as reductants [89 - 90].

Platinum(IV) complexes, as 'third generation' platinum drugs, may offer the advantage of being able to be taken in an oral form ie. a patient would be able to take a pill at home. This reduces cost and stress for the patient, factors which are also a consideration in the development of new drugs and improved treatment protocols. Side-effects have also shown to be reduced with the platinum(IV) drugs. One speculative model for the observed increase in side-effects when platinum(II) drugs are used, is that in this form the drug may react with other biological nucleophiles before reaching the tumour site. In the case of platinum(IV) drugs, they must initially be reduced to the active platinum(II) species. This means that the drug remains in the inert platinum(IV) form which reduces unwanted interactions of the platinum(II) complexes, and hence leads to fewer side-effects.

Chapter 4 reports on the use of ascorbic acid [91, 93], hydroxylamine hydrochloride [95], iron(II), thiosulfate and Sn(II) [100] as potential electron transfer agents, with *cis*-$[PtCl_4(NH_3)_2]$, *trans*-$[PtCl_4(NH_3)_2]$ and $[PtCl_6]^{2-}$ as model platinum(IV) systems. Ascorbic acid was selected as an example of a biological reducing agent, while the other reductants were chosen because of their chemical significance in an effort to elucidate the nature of the underlying redox mechanism.

4.2 EXPERIMENTAL

4.2.1 Materials

The platinum(IV) complexes *cis*-$[PtCl_4(NH_3)_2]$, *trans*-$[PtCl_4(NH_3)_2]$ and $K_2[PtCl_6]$ were commercially available (Strem Chemical Company) and used as supplied. All other chemicals were AnalaR or best reagent grade available.

4.2.1.1 Sn(II)

Solutions of the three platinum(IV) complexes were prepared in 1 M HCl (5 mg/50 mL, *cis*-$[PtCl_4(NH_3)_2]$ 0.27 mM, *trans*-$[PtCl_4(NH_3)_2]$ 0.27 mM, $K_2[PtCl_6]$ 0.21 mM). Tin(II) solutions were freshly prepared from $SnCl_2$ in 1 M HCl and concentrations determined iodometrically [144b].

4.2.1.2 Ascorbic acid

Solutions of all three complexes were prepared in 0.1 M NaCl (5 mg/50 mL, *cis*-$[PtCl_4(NH_3)_2]$ 0.27 mM, *trans*-$[PtCl_4(NH_3)_2]$ 0.27 mM, $K_2[PtCl_6]$ 0.21 mM). Ascorbic acid solutions were prepared in 0.1 M NaCl and the pH adjusted to 4.0 using $HClO_4$. The concentration of ascorbic acid was determined by titration with iodine solution.

4.2.1.3 Fe(II)

Solutions of platinum(IV) complexes *cis*-$[PtCl_4(NH_3)_2]$, *trans*-$[PtCl_4(NH_3)_2]$ (5 mg/50 mL 1 M HCl, 0.27 mM) and $[PtCl_6]^{2-}$ (5 mg/50 mL 1 M HCl, 0.21 mM) were prepared. $[PtCl_6]^{2-}$ solutions (5 mg/50 mL) were also prepared in 0.1 M HCl and 1.0 M $HClO_4$. Freshly made iron(II) solutions were prepared in the same media as the platinum(IV) complexes from $(NH_4)_2Fe(SO_4)_2.6H_2O$.

4.2.1.4 Hydroxylamine hydrochloride

The platinum(IV) complexes (5 mg/50 mL, *cis*-$[PtCl_4(NH_3)_2]$ 0.27 mM, *trans*-$[PtCl_4(NH_3)_2]$ 0.27 mM, $[PtCl_6]^{2-}$ 0.21 mM) were dissolved in 0.1 M NaCl. Hydroxylamine hydrochloride solutions were also prepared in 0.1 M NaCl.

4.2.1.5 $Na_2S_2O_3$

All three platinum(IV) complexes were prepared in 0.1 M NaCl (25 mg/50 mL, *cis*-$[PtCl_4(NH_3)_2]$ 1.35 mM, *trans*-$[PtCl_4(NH_3)_2]$ 1.35 mM, $[PtCl_6]^{2-}$ 1.03 mM). Sodium thiosulfate solutions were also prepared in 0.1 M NaCl.

4.2.2 Reduction Kinetics

Most reactions were monitored at fixed wavelengths using a Perkin Elmer λ-2 Recording Spectrophotometer, but the rapid reduction of both *cis*-$[PtCl_4(NH_3)_2]$ and *trans*-$[PtCl_4(NH_3)_2]$ by sodium thiosulfate was studied using an Applied Photo-Physics Biosequential SX-18MV Stopped-Flow Reaction Analyser. All reactions were followed for 6 - 8 half-lives and the pseudo-first-order ([reducing agent] ≥ 10[Pt(IV)]) rate constants (k_{obs}) calculated using 20 - 30 data points over this interval. The effect of temperature on the reaction rate was also determined and the appropriate activation parameters calculated from these data.

4.2.2.1 Sn(II), Fe(II), $Na_2S_2O_3$ as reducing agents

Plots of k_{obs} *vs* [reducing agent] were linear with zero intercept allowing calculation of the second order rate constant from the expression $k_2 = k_{obs}$[reducing agent]$^{-1}$.

4.2.2.2 Ascorbic acid, hydroxylamine hydrochloride as reducing agents

Plots of k_{obs} *vs* [reducing agent] were non-linear and reached saturation values at high concentrations of reducing agent, but reciprocal plots (k_{obs}^{-1} *versus* [reducing agent]$^{-1}$) were linear. Values of k_{et} (the rate of electron transfer) and K_{OS} (constant for the formation of the outer-sphere encounter complex) were calculated from these data using a non-linear least squares programme or from the slopes and intercepts of the reciprocal plots. Of these two methods the non-linear least-squares technique is the more accurate. For these calculations a spreadsheet programme (Microsoft Excel) was used to fit the raw experimental data to a non-linear equation. Double reciprocal plots weight low values very severely, often by a factor of one hundred which greatly magnifies any errors.

4.3 RESULTS AND DISCUSSION

4.3.1 Tin(II)

Preliminary investigations showed that in the presence of excess Sn(II) in 1.0 M HCl, the absorption spectrum of the octahedral platinum(IV) complexes (also in 1.0 M HCl), slowly changed to that of the corresponding square-planar platinum(II) complex (Equation (4.1)). At longer times, further reduction or complexation occurred which produced absorption spectral changes consistent with the formation of colloidal precipitates (light scattering) [173].

Absorbance *vs* time data for the first reaction (Equation (4.1)), with Sn(II) in excess, followed first-order kinetics and plots of k_{obs} (s^{-1}) *vs* [Sn(II)] were linear with zero intercept (Figure 4.1).

$$[Pt^{IV}Cl_4(N)_2]^{n-} + Sn(II) \xrightarrow{k_2} [Pt^{II}Cl_2(N)_2]^{m-} + Sn(IV) + 2Cl^- \quad (4.1)$$

(where $(N)_2$ is an ammine ligand or Cl^- for $[PtCl_6]^{2-}$)

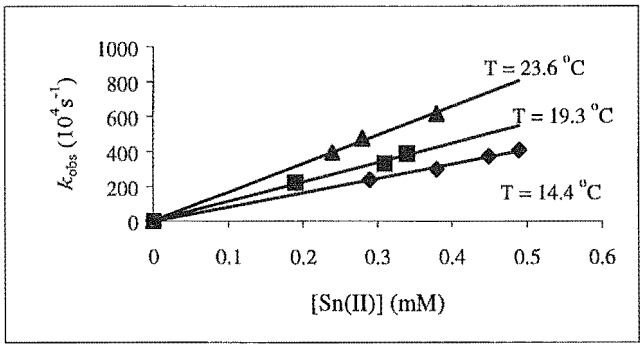
The reactions were sufficiently fast to avoid any major loss of Sn(II) by due to oxidation by dissolved molecular oxygen. Values of k_2 ($M^{-1}s^{-1}$) were obtained from the expression $k_2 = k_{obs}[Sn(II)]^{-1}$ (Table 4.1). Raw data are presented in Table A4.1.

Variation of $[H^+]$ (using $HClO_4$) and $[Cl^-]$ (using NaCl), both at I = 1.0 M, showed that the reaction rate was independent of $[H^+]$ (0.1 - 1.0 M) but increased as the $[Cl^-]$ was increased. Plots of k_{obs} *vs* $[Cl^-]$ were linear with a zero intercept suggesting the general rate law (4.2) with $k_3 \approx 0$.

$$-d[Pt(IV)]/dt = \{k_3 + k_4[Cl^-]\}[Pt(IV)][Sn(II)] \quad (4.2)$$

All subsequent measurements were made in 1.0 M HCl so that $k_2 = k_{Sn} = k_4[Cl^-]$.

Figure 4.1: Plot of k_{obs} *vs* [Sn(II)] for the reduction of *cis*-$[PtCl_4(NH_3)_2]$ by Sn(II).



The above observations are entirely consistent with an earlier investigation of the reaction between $[Pt^{IV}Cl_6]^{2-}$ and Sn(II) [103] and the agreement between the reported kinetic parameters for this reaction and those obtained here, is most satisfactory (Table 4.1). When platinum(II) complexes are used as reducing agents

for platinum(IV), a rate law similar to (4.2) is also observed, and for most of these reactions $k_3 \sim 0$ [100].

Table 4.1: Activation parameters for the reduction of platinum(IV) complexes by Sn(II) (25 °C).

Complex	k_2 ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})
$[PtCl_6]^{2-}$ [a]	308	31.0 ± 1	-93 ± 3
$[PtCl_6]^{2-}$ [b]	378	29 ± 1	-101 ± 3
cis-$[PtCl_4(NH_3)_2]$ [a]	177	50 ± 3	-35 ± 9
trans-$[PtCl_4(NH_3)_2]$ [a]	131	49 ± 1	-39 ± 3

[a] 1.0 M HCl. [b] Ref. [103], 1.0 M HCl.

Of the three platinum(IV) complexes studied, the neutral *cis*- and *trans*-$[PtCl_4(NH_3)_2]$ were reduced at very similar rates (Table 4.1), at about half that observed for $[PtCl_6]^{2-}$. Large changes in stereochemistry are expected for both platinum(IV) and Sn(II) once the electron transfer has occurred, with octahedral platinum(IV) producing square-planar platinum(II), and trigonal pyramidal $[Sn^{II}Cl_2(OH_2)_2]$ [174 - 175] producing octahedral $[Sn^{IV}Cl_x(OH_2)_{6-x}]^{(4-x)+}$ [176]. Although $[SnCl_3]^-$ shows little tendency to add additional ligands in the solid state [174] there is the possibility of an atom transfer redox process via a $[L_5Pt–Cl–SnCl_3]^{n-}$ bridge in solution.

The chloride ion dependence is reflected in the pre-equilibrium with added Cl^- increasing the amount of $[SnCl_3]^-$ [100]. This mechanistic scheme follows that proposed by Peloso for the platinum(II) reduction of platinum(IV) [100].

$$[Sn^{II}Cl_2(OH_2)_2] + Cl^- \overset{K}{\rightleftharpoons} [Sn^{II}Cl_3]^- + H_2O \quad (4.3)$$

$$[Sn^{II}Cl_3]^- + [L_4ClPt^{IV}Cl] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [L_4ClPt^{IV}ClSn^{II}Cl_3]^- \quad (4.4)$$

$$[L_4ClPt^{IV}ClSn^{II}Cl_3]^- \xrightarrow{k_{et}} [L_4Pt^{II}] + [Sn^{IV}Cl_4(OH_2)_2] + Cl^- \quad (4.5)$$

$$\begin{aligned} -d[Pt(IV)]/dt &= \frac{k_1 k_{et}}{k_{et} + k_{-1}} [Sn^{II}Cl_3^-][Pt(IV)] \\ &= \frac{k_1 k_{et} K}{k_{et} + k_{-1}} [Cl^-][Sn(II)^-][Pt(IV)] \\ &= k_{Sn}[Sn(II)][Pt(IV)] \end{aligned} \quad (4.6)$$

where $$k_{Sn} = \frac{k_1 k_{et} K}{k_{et} + k_{-1}} [Cl^-] \quad (4.7)$$

4.3.2 Ascorbic acid

Evans and Green [93] have investigated the kinetics of the reaction between CHIP and ascorbic acid. They found a linear dependence on ascorbic acid concentration and plots of [ascorbic acid]$_T$ *vs* k_{obs} (pH unspecified) had a positive intercept that was difficult to accommodate in any plausible mechanistic scheme.

For the model platinum(IV) compounds used in this study, plots of k_{obs} (s^{-1}) *vs* [ascorbic acid]$_T$ (in excess, at pH = 4.0, I = 0.1 M, NaCl) are curved. Raw data are presented in Table A4.2.

There are three possible proton related reactants for the diprotic ascorbic acid (H_2A) [36] namely H_2A, HA^- and A^{2-} (Equations (4.8) and (4.9)), with

dehydroascorbic acid as the reduction product [177].

$$H_2A \rightleftharpoons HA^- + H^+ \qquad K_1 = 6.67 \times 10^{-5} \qquad (4.8)$$

$$HA^- \rightleftharpoons A^{2-} + H^+ \qquad K_2 = 2.69 \times 10^{-12} \qquad (4.9)$$

A general increase in k_{obs} with increasing pH (pH = 4.0 - 6.0, I = 0.1 M NaCl) is observed, suggesting A^{2-} is the dominant reactant in this pH region.

As the pK_1 value of ascorbic acid is close to 4.0, the selected pH is in the ascorbic acid/ascorbate ion buffer region. HA^- is often orders of magnitude more reactive than H_2A and this may cause the rate constants to be extremely pH sensitive in this pH range. Normally one has to go to pH 6.0 to reach a plateau [178] where all the ascorbic acid is in the ascorbate anion form, but if A^{2-} is extremely reactive, the plateau is sometimes obscured.

Increasing ionic strength and $[Cl^-]$ (varied independently at pH = 4.0) caused a decrease in the reaction rate, but both effects are rather weak. All the listed rate constants (k_{obs}, s^{-1}) were obtained at pH = 4.0, I = 0.1 M NaCl.

The curvature in the k_{obs} *vs* $[\text{ascorbic acid}]_T$ plots can be analysed in terms of classical outer-sphere precursor formation, followed by rate-determining electron transfer (Equations (4.10) and (4.11)).

$$Pt(IV) + HA^- \xrightleftharpoons{K_{OS}} \{Pt(IV).HA^-\} \qquad (4.10)$$

$$\{Pt(IV).HA^-\} \xrightarrow{k_{et}} Pt(II) + A^{2-} \qquad (4.11)$$

with rate law (4.12)

$$-d[Pt(IV)]/dt = \frac{K_{OS}k_{et}\,[Pt(IV)][HA^-]}{1 + K_{OS}[HA^-]} \qquad (4.12)$$

Plots of k_{obs}^{-1} *vs* [ascorbic acid]$_T^{-1}$ were linear ([HA^-] is proportional to [ascorbic acid]$_T$ at constant pH). k_{et}^{-1} can be obtained from the intercept and $(k_{et}K_{OS})^{-1}$ from the slope of these plots, or the data can be fitted using non-linear least-squares analysis (Table 4.2).

Table 4.2: Activation parameters for the reduction of platinum(IV) complexes by ascorbic acid (0.1 M NaCl, 25 °C).

Complex	k_{et} (s^{-1})	K_{OS}	$\Delta H^{\#}$ [a] ($kJmol^{-1}$)	$\Delta S^{\#}$ [a] ($JK^{-1}mol^{-1}$)
$[PtCl_6]^{2-}$	0.172	0.65×10^{-3}	78 ± 2	2 ± 5
$[PtCl_6]^{2-}$ [b]	0.673	-	70.8	-23
cis-$[PtCl_4(NH_3)_2]$	8.5×10^{-3}	4.18×10^{-3}	35.7 ± 0.4	-164 ± 1.5
trans-$[PtCl_4(NH_3)_2]$	10×10^{-3}	2.33×10^{-3}	35.7 ± 1	-164 ± 3

[a] For k_{et}. [b] Ref. [94], 0.12 M HCl, 35 °C.

In strong acid, the $K_{OS}[HA^-]$ term in the denominator will become very small relative to 1 and rate law (4.12) simplifies to (4.13)

$$-d[Pt(IV)]/dt = K_1K_{OS}k_{et}[Pt(IV)][H_2A][H^+]^{-1} \quad (4.13)$$

as observed by Mehrotra *et al* [94] for the reduction of $[PtCl_6]^{2-}$ by ascorbic acid in 0.12 M HCl (Table 4.2). The difference in activation enthalpy between the two neutral complexes and the negative hexachloroplatinate may point to different mechanisms. It was found for hexachloroplatinate that the reaction showed a positive salt effect, which suggests that the rate-determining step would involve two similarly charged ions interacting ie. HA^- and $[PtCl_6]^{2-}$. This would produce the ascorbate free radical. A mechanism for this could be:

$$HA^- + Pt^{IV}Cl_6^{2-} \xrightarrow[\text{slow}]{k_2} HA^{\bullet} + Pt^{III}Cl_5^{2-} + Cl^-$$

$$HA^{\bullet} + Pt^{III}Cl_5^{2-} \xrightarrow{\text{fast}} A^{2-} + Pt^{II}Cl_4^{2-} + Cl^-$$

This mechanism also leads to the same rate law (4.13) as above. In a redox process between a transition element and a reducing agent, the formation of a free radical or unstable intermediate, indicative of a one-electron transfer step, is likely to be a more endothermic process than the corresponding two-electron transfer [96]. This may mean that, as for the oxidation of platinum(II) by peroxydisulfate (see Chapter 5), electrostatics play an important role in determining the reaction mechanism.

The effect of pH on the reduction of ascorbic acid, over the pH range (1.0 – 8.0), was recently investigated by House *et al* [92]. The reaction was barely measurable (ie. slow) at pH < 3.0 but once past pH = 4.0, the reaction becomes very fast (ie. requiring stopped-flow techniques). Implications for the biological system mean that at the pH of plasma, ascorbic acid will react quickly with platinum(IV) complexes. As well as being extremely pH sensitive, the reactions needed to be studied in the absence of oxygen and the presence of EDTA to remove any trace metal catalysis. Once these conditions were satisfied the reactions obeyed normal first-order kinetics without 'saturation'. Bose and Weaver [91] have recently published a paper detailing the presence of an ascorbate radical anion being produced in the reaction. They were working in oxygen-free solutions without the presence of EDTA, and were getting very complicated kinetics.

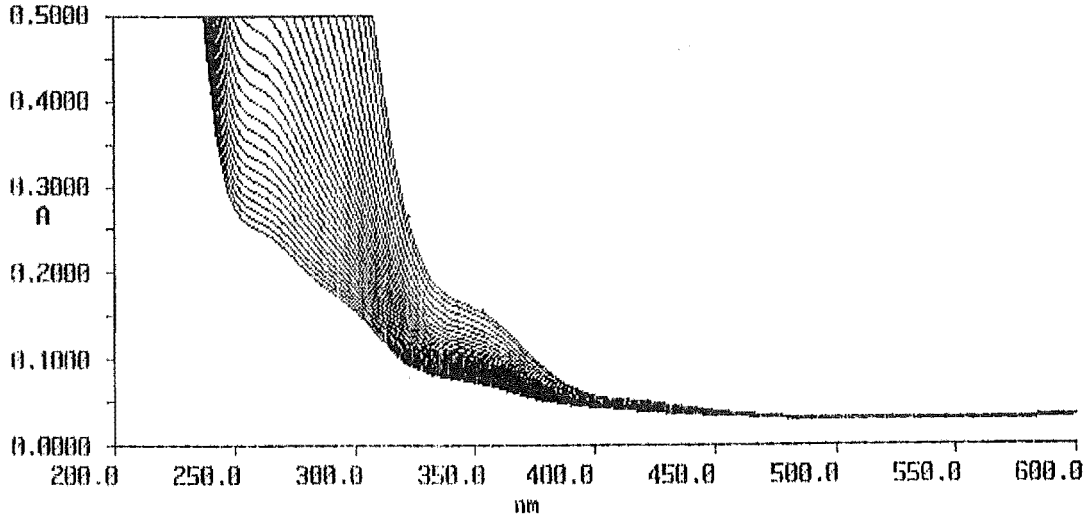
4.3.3 Hydroxylamine hydrochloride

Hydroxylamine is an unstable endoergic compound ($\Delta G_f = +23$ kJmol^{-1}). Its standard reduction potentials indicate that it can act as both an oxidising and reducing agent, but it more readily effects reduction reactions. This reaction does not produce N_2, but instead N_2O is produced in a mechanistically complex reaction.

$$2NH_3OH^+ - 4e \rightarrow N_2O + 6H^+ + H_2O \qquad (4.14)$$

The kinetics of the reduction of $[PtCl_6]^{2-}$ by hydroxylamine hydrochloride have been studied by Sen Gupta *et al* [95]. Their work is reinvestigated here under differing pH conditions and with a wider hydroxylamine concentration range. Data for the reduction of *cis*- and *trans*-$[PtCl_4(NH_3)_2]$ are also reported (Table 4.3). Repeat absorbance scans showed an overall decrease in absorbance (Figure 4.2).

Figure 4.2: Repeat scans (180 s time interval) showing the decrease in absorbance for the reduction of *trans*-$[PtCl_4(NH_3)_2]$ by hydroxylamine (14 mM, 0.1 M NaCl, 40 °C).



In all cases plots of k_{obs} *vs* [hydroxylamine] were curved (Figure 4.3), but reciprocal plots ($1/k_{obs}$ *vs* 1/[hydroxylamine]) were linear with positive y-intercepts.

Raw data are presented in Table A4.3. As for ascorbic acid, these suggest a mechanism involving encounter complex formation prior to electron transfer.

$$Pt(IV) + NH_2OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \{Pt(IV).NH_2OH\} \xrightarrow{k_{et}} Pt(II) + \text{oxidation products} \qquad (4.15)$$

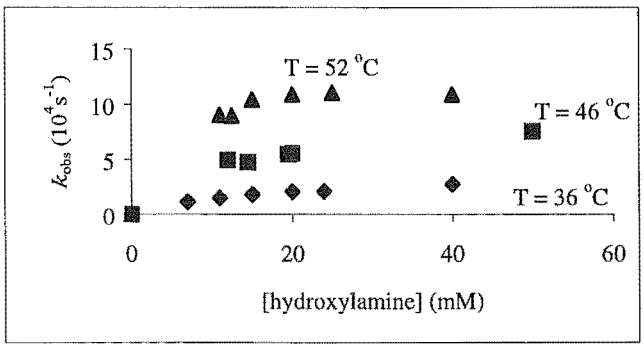
$$NH_3OH^+ \overset{K_a}{\rightleftharpoons} NH_2OH + H^+ \qquad (4.16)$$

Equations (4.15) and (4.16) give rise to the rate law (4.17)

$$\text{rate} = \frac{k_1 k_{et} K_a}{k_{-1} + k_{et}} \left\{ \frac{[Pt(IV)][NH_3OH^+]}{[H^+]} \right\} \qquad (4.17)$$

which shows the inhibitory effect of H^+, suggesting that it is the unprotonated form of hydroxylamine that is the reactive species in solution. k_{et} (the rate of electron transfer) and K_{OS} (the constant for the formation of the outer-sphere encounter complex) can be calculated from the reciprocal plots (where k_{et} = (intercept)$^{-1}$ and $k_{et}K_{OS}$ = (slope)$^{-1}$) or by non-linear least-squares analysis.

Figure 4.3: Plot of k_{obs} *vs* [hydroxylamine] for the reduction of *cis*-$[PtCl_4(NH_3)_2]$ by hydroxylamine.



An outer-sphere mechanism is favoured as the possibility of bridging in the transition state is unlikely.

Table 4.3: Activation parameters for the reduction of platinum(IV) complexes by hydroxylamine (0.1 M NaCl, 25 °C).

Complex	k_{et} (s^{-1})	K_{OS}	$\Delta H^{\#}$ [a] ($kJmol^{-1}$)	$\Delta S^{\#}$ [a] ($JK^{-1}mol^{-1}$)
$[PtCl_6]^{2-}$	4.33×10^{-4}	155	64 ± 2	-95 ± 6
$[PtCl_6]^{2-}$ [b]	-	-	68.6 ± 2	-80 ± 6
cis-$[PtCl_4(NH_3)_2]$	1.21×10^{-4}	47.5	72.8 ± 0.5	-76 ± 1.5
trans-$[PtCl_4(NH_3)_2]$	5.12×10^{-4}	55.8	48.1 ± 0.2	-147 ± 1

[a] For k_{et}. [b] Ref. [95], pH = 4.8, 35 °C.

4.3.4 Iron(II)

Iron is a trace metal found in the body. It is incorporated into haemoglobin, which is used for transporting oxygen around the body. It has two main oxidation states, Fe^{2+} and Fe^{3+}. This opens up the area of redox chemistry – with iron being both a reductant (Fe^{2+}) and oxidant (Fe^{3+}). Peloso has done some research into platinum redox kinetics with Fe(II). He has concentrated on studying the role of steric hindrance on a range of reactions and has used iron(II) as a reducing agent in one major study [100]. In his work he used ferrocene in organic solvents as the reductant. This differs greatly from the research presented here which used ferrous ammonium sulfate in aqueous solution. In this research it was decided to study the reduction of platinum(IV) by iron(II) to allow comparison with the biological reducing agent ascorbic acid, and to see if a one-electron reductant would have any effect on the reaction mechanism.

The reduction of $[PtCl_6]^{2-}$ was studied in three different media (1.0 M HCl, 0.1 M HCl and 1.0 M $HClO_4$) whereas *cis*- and *trans*-$[PtCl_4(NH_3)_2]$ were only studied in 1.0 M HCl. With Fe(II) in HCl the absorbance of all three complexes increased over time to a different constant value for each complex. However a different pattern was seen for $[PtCl_6]^{2-}$ and Fe(II) in $HClO_4$, where the absorbance decreased over time. The second order rate constant, k_2, for the reduction of Pt(IV) by Fe(II) can be found from the slope of the k_{obs} *vs* [Fe(II)] plot ie. $k_2 = k_{obs}[Fe(II)]^{-1}$. Data are presented in Table A4.4. The similarity of all activation parameters points to a common mechanism (Table 4.4). This could involve two one-electron transfer steps following the formation of a bridged species where, in the case of perchloric acid, x=0. Only a small variation in rate with $[Cl^-]$ was observed.

$$Pt^{IV}\text{-}Cl + [Fe^{II}(OH_2)_yCl_x]^{n+} \rightleftharpoons [Pt^{IV}\text{-}Cl\text{-}Fe^{II}(OH_2)_{y-1}Cl_x]^{m+} + H_2O \quad (4.18)$$

The rate law for the bimolecular process is:

$$\text{rate} = k_2[Pt(IV)][Fe(II)] \quad (4.19)$$

Table 4.4: Activation parameters for the reduction of platinum(IV) by iron(II) (25 °C).

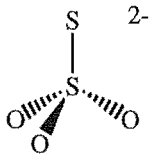
Complex	k_2 ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ ($kJmol^{-1}$)	$\Delta S^{\#}$ ($JK^{-1}mol^{-1}$)
$[PtCl_6]^{2-}$ [a]	0.274	59 ± 2	-59 ± 6
$[PtCl_6]^{2-}$ [b]	0.132	58 ± 2	-67 ± 6
$[PtCl_6]^{2-}$ [c]	0.158	50 ± 2	-91 ± 6
cis-$[PtCl_4(NH_3)_2]$ [a]	1.21×10^{-3}	82 ± 3	-34 ± 9
trans-$[PtCl_4(NH_3)_2]$ [a]	1.54×10^{-3}	79 ± 2	-26 ± 6

[a] 0.1 M HCl. [b] 1.0 M HCl. [c] 1.0 M $HClO_4$.

This is a mechanism similar to that proposed by Peloso for the reduction of Pt(IV) by ferrocene in methanolic solutions [175].

4.3.5 Thiosulfate

There are a wide range of sulfur oxoanions, many of which are important in both the laboratory and industry. The sulfur in thiosulfate ($S_2O_3^{2-}$) has an oxidation number of two, but the environments of the two S atoms are quite different.

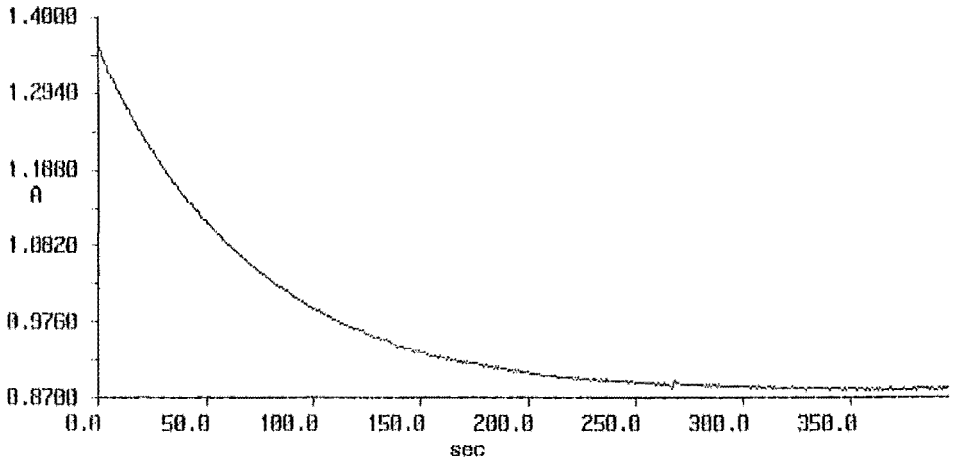


thiosulfate

It is a mild reducing agent and generally reacts via two-electron transfer steps with an oxygen-transfer pathway. Likely reaction products from thiosulfate reduction will be the corresponding platinum(II) product and dithionate ($S_4O_6^{2-}$).

The model platinum(IV) complexes were reacted with thiosulfate in 0.1 M NaCl. All three complexes showed a decrease in absorbance, reaching a constant infinity value (Figure 4.4).

Figure 4.4: Absorbance *vs* time curve for the reduction of $[PtCl_6]^{2-}$ by thiosulfate (27.5 mM, 0.1 M NaCl, 390 nm, 25 °C).



The reduction of the three model platinum(IV) complexes by thiosulfate has the rate law

$$\text{rate} = k_2[\text{Pt(IV)}][\ S_2O_3^{2-}] \qquad (4.20)$$

with $k_2 = k_{obs}[S_2O_3^{2-}]^{-1}$.

The rate of reduction of $[PtCl_6]^{2-}$ was considerably slower than the reduction of the neutral *cis*- and *trans*-$[PtCl_4(NH_3)_2]$ due to the less favourable reaction between two negatively charged species (Table 4.5). This electrostatic repulsion accounts for the more negative activation entropy associated with $[PtCl_6]^{2-}$. Data are presented in Table A4.5.

The mechanism for thiosulfate reduction will most probably involve a two-electron transfer step via an outer-sphere mechanism. The product will be the related platinum(II) species, the platinum(IV) having lost two chloride ions.

$$[PtCl_6]^{2-} + S_2O_3^{2-} \rightarrow [Cl_5PtCl\cdots S_2O_3]^{4-} \rightarrow [PtCl_4]^{2-} + \text{oxidation products} \qquad (4.21)$$

Table 4.5: Activation parameters for the reduction of platinum(IV) complexes by $S_2O_3^{2-}$ (0.1 M NaCl, 25 °C).

Complex	k_2 ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ ($kJmol^{-1}$)	$\Delta S^{\#}$ ($JK^{-1}mol^{-1}$)
$[PtCl_6]^{2-}$	0.567	40 ± 2	-117 ± 6
cis-$[PtCl_4(NH_3)_2]$	15.7	62 ± 1	-15 ± 3
trans-$[PtCl_4(NH_3)_2]$	11.7	59.7 ± 0.5	-24 ± 2

No chloride ion effect in the reduction of $[PtCl_6]^{2-}$ was found, but a positive salt effect was observed, as expected for a reaction between ions of the same charge.

4.3.6 Correlation with reduction potential

The rate of a reaction can often be correlated with the reduction potential for the reaction. It was decided to compare the rate of reduction of hexachloroplatinate with the reduction potential of three of the reducing agents to see if there are any trends in reactivity.

Table 4.6: Correlation of rate constant with reduction potential.

k_{red} (25 °C)	Reduction potential	
308 $M^{-1} s^{-1}$	$Sn^{4+} + 2e \rightarrow Sn^{2+}$	0.151 V
0.567 $M^{-1}s^{-1}$	$S_4O_6^{2-} + 2e \rightarrow 2S_2O_3^{2-}$	0.08 V
0.274 $M^{-1} s^{-1}$	$Fe^{3+} + e \rightarrow Fe^{2+}$	0.771 V

As can be seen from Table 4.6, there appears to be no correlation between rate and redox potential. If the two-electron transfer agents are considered (Sn^{2+} and $S_2O_3^{2-}$) the order holds ie. Sn(II) is a 'better' reducing agent and it has the higher reduction potential. Fe(II) is a one-electron reducing agent and this may be one reason why the correlation does not hold for all complexes.

4.3.7 Other reductants

Other unsuccessful reductants investigated included hydroquinone, I^-, oxalate and sulfite. Cysteine was also evaluated as a reducing agent without success. This is thought to be due to the pH (0.1 M NaCl, pH = 7.45) at which the reaction was studied. After this work was completed two papers by Elding *et al* [89 - 90] were published detailing the reduction of platinum(IV) by R-(+)-(L)-cysteine, glutathione,

penicillamine, L-methionine and thioglycolic acid. These reaction rates were found to be very sensitive to acid conditions. This provides an explanation as to why no reaction was observed. In fact, the reaction was very fast and thus had instantly gone to completion under the conventional mixing techniques used.

4.4 CONCLUSIONS

There is much speculation in the literature as to the role of platinum(III) in the two-electron transfer Pt(II) / Pt(IV) redox system. The reductants and oxidants used in this study have been either one-electron (non-complementary) or two-electron (complementary) acceptors. The reducing agents Sn(II), ascorbic acid, hydroxylamine hydrochloride and thiosulfate are all two-electron donors and no reason is seen to postulate any mechanism other than direct two-electron transfer except for the reduction of hexachloroplatinate by Sn(II). The other systems do however differ in detail, as the Sn(II) and Fe(II) reductions are proposed to proceed via $[PtCl_6]^{2-}$ substitution into the labile reductant coordination sphere ie. an inner-sphere mechanism. An outer-sphere activated complex is proposed for the ascorbic acid and hydroxylamine reductions of inert platinum(IV).

The *in vivo* reduction of platinum(IV) anti-tumour drugs is thought to be their primary mode of action. This study measured the rates of reduction of platinum(IV) complexes to attempt to determine if *in vivo* reduction is a viable pathway. Only one biological reducing agent (ascorbic acid) was used, other reductants were used to explore mechanistic differences. Ascorbic acid effects reduction of platinum(IV) at a rate that would allow *in vivo* reduction to proceed. However there are other, more plentiful biological reductants (ie. glutathione, cysteine) which have been studied by other groups. Results from these studies show that ascorbic acid and thiol-containing

complexes are effective reducing agents and thus it seems likely, considering all the chemical and biochemical research, that platinum(IV) compounds may act as prodrugs for the anti-tumour active platinum(II) complexes.

CHAPTER 5

THE OXIDATION OF PLATINUM(II) COMPLEXES

5.1 INTRODUCTION

Since the discovery of the anti-tumour activity of *cis*-diamminedichloro-platinum(II), there has been significant interest in the chemistry of simple four-coordinate square-planar platinum(II) complexes [21, 36, 179].

Several thousand potentially active platinum(II) complexes have now been tested for anti-tumour properties [21]. It has been established that the early structure-activity relationships which were developed to correlate biological success and structure, do not always apply [21]. For example, the ligands on carboplatin, diammine(cyclobutane-1,1-dicarboxylato)platinum(II), are many orders of magnitude more inert [145, 180 - 181] than those for cisplatin [44 - 51], yet both are successful anti-tumour drugs.

A further generalisation that has recently been challenged is that the platinum must be in the II+ oxidation state. CHIP, *cis, cis ,trans*-[$Pt^{IV}Cl_2(iPrNH_2)_2(OH)_2$] [36, 85, 93], tetraplatin, [$Pt^{IV}Cl_4$(chxn)] [21, 36], and JM-216, *cis, trans, cis*-[$Pt^{IV}Cl_2(OAc)_2(NH_3)$(cyclohexylamine)] [21, 170] all show particular promise as anti-tumour drugs. The general route for the synthesis of these complexes involves the oxidation of a suitable platinum(II) precursor compound. It is thus important to understand the processes by which the oxidation occurs.

The oxidation of square-planar platinum(II) complexes can occur by two main mechanisms. The first is a simple two-electron transfer ie. a complementary redox process. The second mechanism proceeds by two successive one-electron transfers requiring the production of a platinum(III) intermediate. This species is unstable but has been detected by addition of a radical trapping agent (eg. galvinoxyl) to a reaction mixture [105]. This does not distinguish platinum(III) from any other radical and in this situation other radicals including the peroxydisulfate radical anion and the hydroxyl radical may be detected.

In order to study reactions of platinum(IV) complexes it is necessary to prepare the compounds by the oxidation of platinum(II) complexes. Little work has been done on the kinetics of the oxidation process (Ref. [105 - 113, 115 - 116, 172]) and so this research has measured kinetic data for the oxidation of platinum(II) complexes using potassium permanganate, potassium dichromate, hydrogen peroxide and sodium peroxydisulfate as oxidising agents.

5.2 EXPERIMENTAL

5.2.1 Materials

The platinum(II) complexes were either commercially available from Strem Chemical Company (cisplatin, carboplatin, $[PtCl_2chxn]$, $K_2[PtCl_4]$, $K_2[Pt(ox)_2]$, $K_2[Pt(en)_2]$, $K_2[Pt(NH_3)_4]$) and used without further purification, or synthesised ($K_2[PtCl_2(ox)]$) by known methods [107]. For the latter complex, a ^{195}Pt NMR spectrum (δ = -995 ppm, referenced to H_2PtCl_6) was in agreement with the literature value (-1005 ppm [107]). All other chemicals used ($KMnO_4$, $K_2Cr_2O_7$, $Na_2S_2O_8$, H_2O_2) were AnalaR or best reagent grade available.

5.2.1.1 $Na_2S_2O_8$

Solutions of cisplatin (25 mg/50 mL 1 M HCl, 1.67 mM), carboplatin (25 mg/50 mL H_2O, 1.35 mM), $K_2[PtCl_2(ox)]$ (3 mg/50 mL H_2O, 0.14 mM), $K_2[Pt(ox)_2]$ (3 mg/200 mL H_2O, 0.03 mM), $K_2[PtCl_2(ox)]$ (25 mg/50 mL 1 M HCl, 1.20 mM), $K_2[Pt(en)_2]$ (25 mg/50 mL 1 M HCl, 1.29 mM) and $K_2[Pt(NH_3)_4]$ (25 mg/50 mL 1 M HCl, 1.42 mM) were prepared. $[PtCl_2(chxn)]$ (1 mg, 0.43 mM) was dissolved in three drops of DMF before addition of 10 mL $S_2O_8^{2-}$ solution (1 M HCl). Reactions involving DMF and $S_2O_8^{2-}$ and DMF and platinum(II) were performed to confirm that DMF had no effect on the reaction rate. The $Na_2S_2O_8$ solution was freshly prepared (in 1 M HCl for cisplatin, $[Pt(en)_2]^{2+}$, $[Pt(NH_3)_4]^{2+}$, $[PtCl_4]^{2-}$ and in 2 M HCl for $[PtCl_2(ox)]^{2-}$, carboplatin, $[Pt(ox)_2]^{2-}$) before each kinetic run.

5.2.1.2 H_2O_2

Solutions of carboplatin (50 mg/50 mL H_2O, 2.70 mM), $K_2[Pt(ox)_2]$ (10 mg/25 mL H_2O, 0.89 mM), $K_2[Pt(en)_2]$ (30 mg/50 mL 1 M $HClO_4$, 1.55 mM) and $K_2[Pt(NH_3)_4]$ (30 mg/50 mL 1 M $HClO_4$, 1.70 mM) were prepared. H_2O_2 was freshly prepared (in 2 M $HClO_4$ for carboplatin, $[Pt(ox)_2]^{2-}$ and in 1 M $HClO_4$ for $[Pt(en)_2]^{2+}$, $[Pt(NH_3)_4]^{2+}$) and the concentration determined by titration with potassium permanganate solution, standardised using AR sodium oxalate. Cisplatin (1 mg, 0.33 mM) and $[PtCl_2(chxn)]$ (1 mg, 0.43 mM) were dissolved in three drops of DMF (it was determined that DMF had no effect on the reaction rate) before addition of 10 mL of H_2O_2 solution (1 M $HClO_4$). $[PtCl_4]^{2-}$ (1 mg, 0.24 mM) was dissolved in a drop of water before addition of 10 mL of H_2O_2 (1 M $HClO_4$).

5.2.1.3 $KMnO_4$

Solutions of $[Pt(NH_3)_4]^{2+}$, $[Pt(en)_2]^{2+}$ and $[PtCl_4]^{2-}$ were prepared immediately prior to reaction by dissolving known amounts in 0.1 M $HClO_4$. Solutions of carboplatin were prepared in water. $KMnO_4$ solution (2 mg/100 mL , 0.126 mM in 0.1 M $HClO_4$ for $[Pt(NH_3)_4]^{2+}$, $[Pt(en)_2]^{2+}$, $[PtCl_4]^{2-}$ and in 0.2 M $HClO_4$ for carboplatin) was used.

5.2.1.4 $K_2Cr_2O_7$

Solutions of carboplatin and $[PtCl_4]^{2-}$ were prepared immediately prior to reaction in 1.0 M $HClO_4$. $K_2Cr_2O_7$ solution (7.4 mg/250 mL 1M $HClO_4$, 1.0×10^{-4} M) was used.

5.2.2 Oxidation kinetics

The reactions in this chapter were monitored at fixed wavelengths using UV/Visible spectroscopy. All reactions except those involving permanganate, were followed using a Perkin Elmer λ-2 Recording Spectrometer. For low temperature reactions this was fitted with a 5 cm pathlength jacketed cell attached to an external cooling (waterbath) system. A refrigerator unit immersed in the water bath allowed temperatures as low as 12 °C to be reached. For systems requiring temperatures of greater than 30 °C an electrically heated cell unit, with a 4 cm pathlength cell, was used.

Due to the rapidity of the permanganate oxidation reactions, these were studied with an Applied Photo-Physics Biosequential SX-18MV Stopped-Flow Reaction Analyser.

In all cases the reactions were monitored at fixed wavelengths for 6 - 8 half-lives and the appropriate rate constants calculated using at least 20 - 30 data points over that time interval. The effect of temperature was studied to allow calculation of activation parameters. All rate data are presented in Tables A5.1 – A5.6.

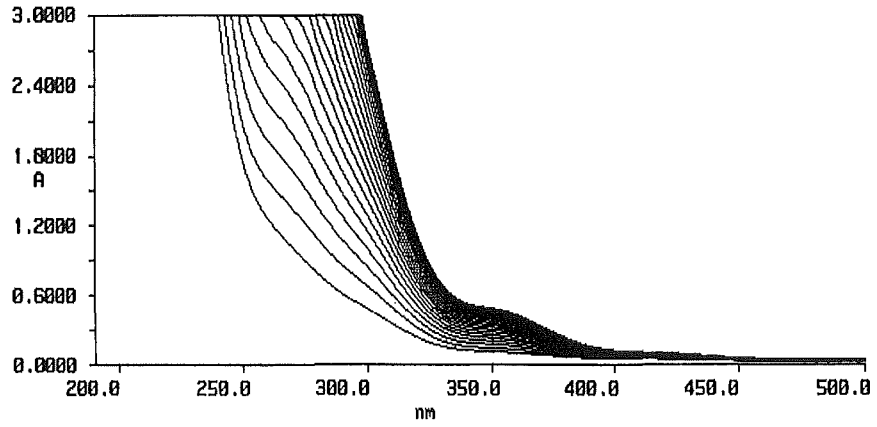
5.3 RESULTS AND DISCUSSION

5.3.1 Peroxydisulfate Oxidation

Peroxydisulfate, $S_2O_8^{2-}$, is a powerful oxidising agent in aqueous solution but, even with strong reducing agents, reactions are usually slow [182 - 183]. In contrast, the $S_2O_8^{2-}$ / $[Pt(NH_3)_4]^{2+}$ oxidation takes place in the stopped-flow time scale [105]. This oxidation work by Harrigan and Johnson [105] was repeated under different conditions, and the oxidation of $[Pt(en)_2]^{2+}$ studied using stopped-flow techniques. Neutral and negatively charged complexes were also studied to see the effect of charge on rate and mechanism.

Peroxydisulfate oxidations of the neutral platinum(II) anti-cancer drugs, cisplatin, $[PtCl_2(chxn)]$ and carboplatin, were followed using conventional mixing spectrophotometric techniques. As with $[Pt(NH_3)_4]^{2+}$, the absorbance of the reaction mixture ($[Pt(II)] \sim 0.1$ mM, $[S_2O_8^{2-}] = 10 - 50$ mM, $[H^+] = 1.0$ M) increased with time at all wavelengths below 350 nm to reach a stable final absorbance without the generation of isosbestic points (Figure 5.1).

Figure 5.1: Repeat scans (180 s time interval) showing the increase in absorbance for the oxidation of carboplatin by peroxydisulfate (10 mM, 1 M HCl, 30 °C).



Absorbance *vs* time traces at fixed wavelengths followed pseudo-first-order kinetics and plots of k_{obs} (s^{-1}) *vs* [$S_2O_8^{2-}$] were linear with zero intercept (Figure 5.2).

Values of k_2 in the expression

$$-d[Pt(II)]/dt = k_2[Pt(II)][S_2O_8^{2-}] \quad (5.1)$$

were calculated from

$$k_2 = k_{obs}[S_2O_8^{2-}]^{-1} \quad (5.2)$$

and all k_2 data at various temperatures were used to estimate the activation parameters ($\Delta H^{\#}$ and $\Delta S^{\#}$) in Table 5.1.

Figure 5.2: k_{obs} *vs* [$S_2O_8^{2-}$] for the oxidation of carboplatin by peroxydisulfate (22.5 °C, 1.0 M $HClO_4$).

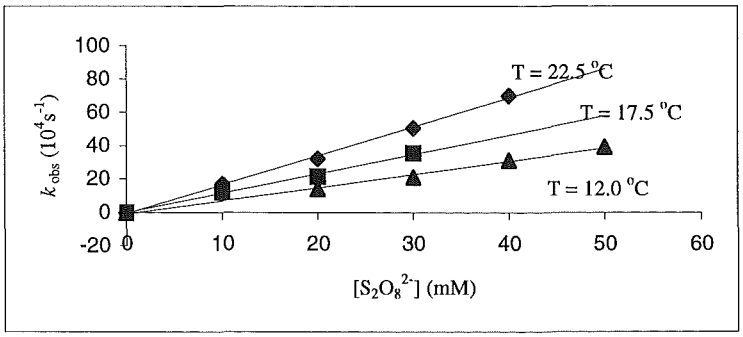


Table 5.1: Activation parameters for the oxidation of platinum(II) complexes by peroxydisulfate (25 °C).

Complex	k_x [a]	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})
$[Pt(ox)_2]^{2-}$ [b]	1.94 s^{-1}	85.7 ± 4	48 ± 12
$[PtCl_2(ox)]^{2-}$ [b]	0.431 s^{-1}	80.8 ± 6	19 ± 18
$[PtCl_4]^{2-}$ [b]	0.0056 s^{-1}	105 ± 3	66 ± 9
$[PtCl_4]^{2-}$ [c]	28 M^{-1}s^{-1}	94.2 ± 3	66 ± 9
cis-$(NH_3)_2$ [b]	0.028 M^{-1}s^{-1}	37.9 ± 2	-147 ± 6
chxn [b]	0.113 M^{-1}s^{-1}	53.1 ± 3	-85 ± 9
carboplatin [d]	0.205 M^{-1}s^{-1}	54.0 ± 3	-77 ± 9
$[Pt(en)_2]^{2+}$ [b]	10.14 M^{-1}s^{-1}	44.0 ± 2	-78 ± 6
$[Pt(NH_3)_4]^{2+}$ [b]	2.58 M^{-1}s^{-1}	28.0 ± 1	-143 ± 3
$[Pt(NH_3)_4]^{2+}$ [e]	4.23 M^{-1}s^{-1}	39.3	-101
$[Fe(OH_2)_6]^{2+}$ [f]	137 M^{-1}s^{-1}	48.0	-43

[a] See text for rate laws. [b] 1.0 M HCl. [c] Data for the Cu^{2+} catalysed oxidation. [d] 1.0 M $HClO_4$. [e] Ref. [105], I = 1.0 M $HClO_4$. [f] Ref. [184], I = 1.0 M.

With the anionic complexes $[PtCl_4]^{2-}$, $[Pt(ox)_2]^{2-}$ and $[PtCl_2(ox)]^{2-}$, the absorbance (250 - 400 nm) of the reaction mixture (Pt(II) ~ 0.01 mM, $[PtCl_4^{2-}]$ ~ 1 mM, $[S_2O_8^{2-}]$ = 0.2 - 50 mM, [HCl] = 1.0 M) again increased to a constant value without isosbestic points. However, absorbance *vs* time plots at fixed wavelengths were linear indicating the reaction is pseudo-zero-order in platinum(II) (Figure 5.3). Experiments varying the $[Pt(II)]_{initial}$ showed that the reaction was independent of the initial [Pt(II)]. The end point times of the reactions were proportional to $[S_2O_8^{2-}]$ and so rate law (5.3) is followed for these anionic systems.

$$-d[Pt(II)]/dt = k_0[S_2O_8^{2-}] = k^{\circ}_{obs}\ (M\ s^{-1}) \qquad (5.3)$$

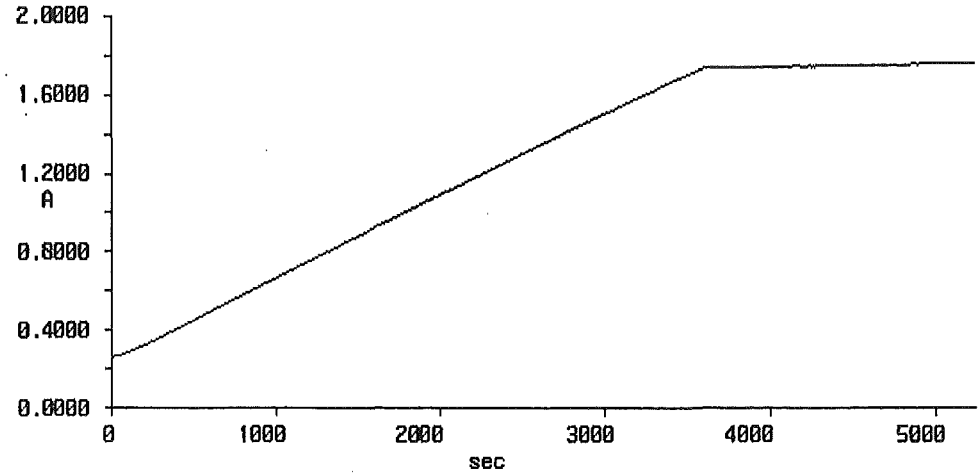
Values of k_0 (s^{-1}) were calculated from the expression (5.4).

$$k_0 = k^{\circ}_{obs}[S_2O_8^{2-}]^{-1} \quad (5.4)$$

Activation parameters were estimated from the variation of k_0 with temperature (Table 5.1).

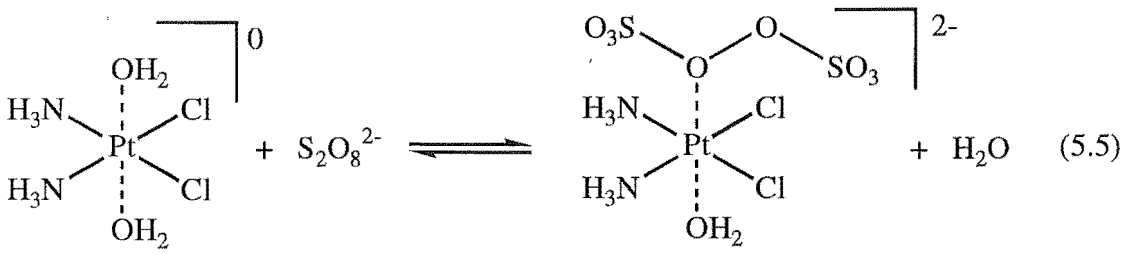
The changing reaction order between $S_2O_8^{2-}$ and platinum(II) complexes of differing charge suggests that electrostatic interactions are significant. Neutral and positively charged platinum(II) complexes exhibit rates that depend on both [Pt(II)] and [$S_2O_8^{2-}$], while anionic platinum(II) complexes react at rates independent of [Pt(II)].

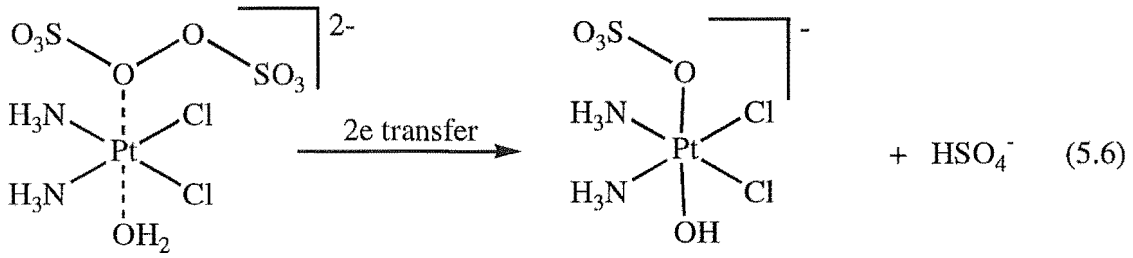
Figure 5.3: Absorbance *vs* time scan for the oxidation of $[PtCl_4]^{2-}$ by peroxydisulfate (20 mM, 1 M HCl, 340 nm, 35.5 °C).



Equations (5.5) and (5.6) provide mechanisms which generate the observed reaction order but involve a direct two-electron transfer. While two-electron transfer processes are not common, the Pt(II)/Pt(IV) redox couple may be one situation where this mechanism is plausible, as the Pt, en and Cl^- exchange rates between $[Pt^{II}(en)_2]^{2+}$

and $[Pt^{IV}Cl_2(en)_2]^{2+}$ all proceed with similar values for the third order rate constant [185].





The proposal for the hydroxo sulfato platinum(IV) product follows from the work of Harrigan and Johnson [105]. In the presence of 1 M HCl, *cis*-$[Pt^{IV}Cl_6]^{2-}$ is the most likely final product.

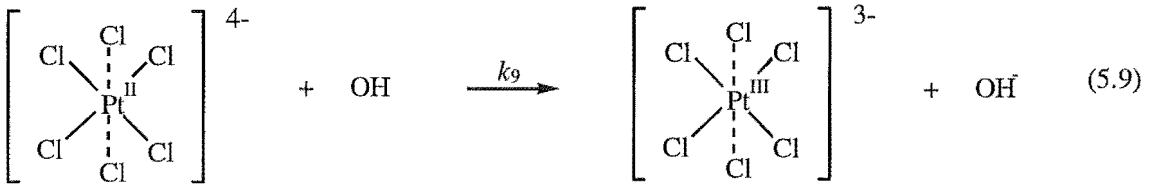
The $[Pt(II)]^{2+}$ / $S_2O_8^{2-}$ reactions are quite rapid for peroxydisulfate but are still not as fast as the $[Fe(II)]^{2+}$ / $S_2O_8^{2-}$ system [184]. Nevertheless, the activation enthalpies for both $[Pt(II)]^{2+}$ and $[Fe(OH_2)_6]^{2+}$ are similar (Table 5.1) suggesting that most of the energy barrier in the oxidation takes place in forming the encounter complex. However, in the post-encounter electron transfer reaction, $[Fe(OH_2)_6]^{2+}$ only requires a one-electron transfer process. This may allow for a more rapid reaction.

For the $[Pt(II)]^{2-}$ complexes that are oxidised at rates independent of the reductant concentration, it is difficult to avoid a mechanism that does not involve

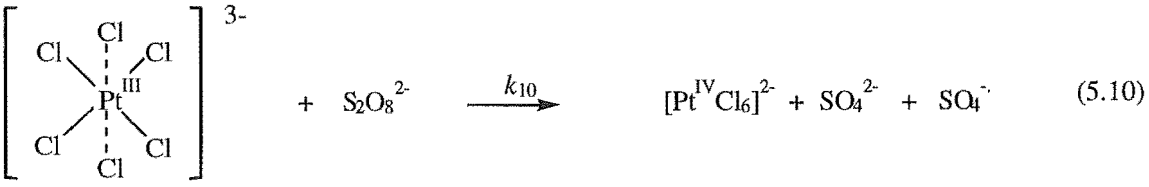
Pt(III), ie. a series of one-electron transfers. Equations (5.7) - (5.11) outline one possible mechanistic scheme via a radical chain process.

$$S_2O_8^{2-} \xrightarrow[\text{slow}]{k_7} 2SO_4^{\cdot-} \qquad (5.7)$$

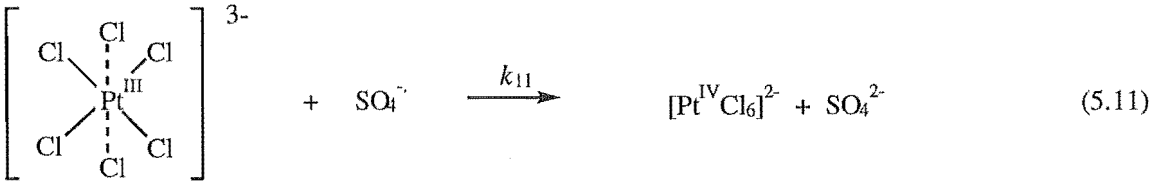
$$SO_4^{\cdot-} + H_2O \xrightarrow{k_8} OH^{\cdot} + SO_4^{2-} \qquad (5.8)$$



(5.9)



(5.10)



(5.11)

Both $[Pt^{IV}Cl_6]^{2-}$ and $[Pt^{IV}Cl_5(OH)]^{-}$ are detected as reaction products by ^{195}Pt NMR (δ = 0.4 ppm, -280 ppm, respectively, relative to H_2PtCl_6). In $HClO_4$ one major peak is observed. This has been tentatively assigned as $[PtCl_4(OH)(SO_4)]^{2-}$ (961 ppm). If the NMR solution is left for a longer period of time (two weeks) further peaks are observed. One of these (1076 ppm) is assigned to the dihydroxoplatinum(IV) complex, formed by substitution of SO_4 by OH. Assuming a steady state concentration of $SO_4^{\cdot-}$, $OH^{\cdot}$ and Pt(III) [182], the mechanistic scheme (5.7 - 5.11) gives:

$$-d[S_2O_8^{2-}]/dt = (k_7k_8k_{10}/k_{11})^{1/2}[S_2O_8^{2-}] \qquad (5.12)$$

Activation parameters for the $S_2O_8^{2-}$ oxidation of $[Pt(II)]^{2-}$ complexes follow a different pattern from those observed for the cationic and neutral platinum systems. These cannot be compared as the reaction orders are different. However, the first three entries in Table 5.1 (negatively charged platinum(II) complexes) have less-favourable electrostatics with which to form any encounter complex and therefore their oxidations occur by a different mechanism. In contrast, the much lower activation enthalpy and significantly more negative activation entropy for the neutral and positively charged complexes are consistent with the association step (5.5) prior to the electron transfer process (5.6). This latter process should not have a high activation barrier and thus is not expected to show a significant entropy effect. So reaction (5.5) is mainly responsible for the activation parameters in the lower part of Table 5.1.

The oxidation of the negatively charged platinum(II) complexes shows a small $[H^+]$ effect (non-linear increase in rate as the concentration increases). Varying the amount of chloride ion in the reaction mixture has no effect on the rate.

For the first-order oxidations (the neutral and positively charged complexes) there is a very slight increase in rate as the $[H^+]$ increases. A chloride ion effect is observed. There is a large decrease in rate when one goes from 0.0 M to 0.1 M Cl^-, but with further increases in $[Cl^-]$ the effect is negligible.

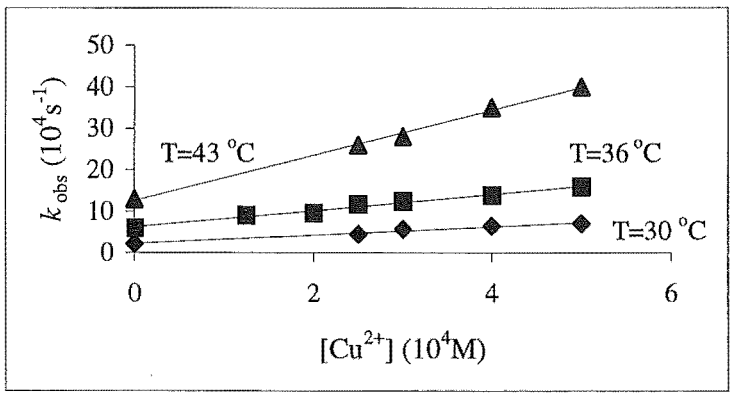
Oxidations involving peroxydisulfate are often subject to trace metal catalysis so it was decided to study the effect of Cu^{2+} on the rate of oxidation of $[PtCl_4]^{2-}$. Zero-order reactions were again observed and it was found that copper(II) does have an acceleratory effect on the rate of oxidation. Plots of k_{obs} *vs* $[Cu^{2+}]$ were linear

with a positive intercept corresponding to the uncatalysed rate (Figure 5.4). Activation entropy calculated from this data is in agreement with that for the uncatalysed rate (Table 5.1). The exact mechanism of catalysis is unknown but is thought to occur by the initial oxidation of Cu^{2+} to Cu^{3+}

$$Cu^{2+} + S_2O_8^{2-} \longrightarrow Cu^{3+} + SO_4^{\cdot-} + SO_4^{2-} \qquad (5.13)$$

which then oxidises the platinum(II) complex. Thus there is competition between Cu^{3+}, $OH^{\cdot}$, $SO_4^{\cdot-}$ and $S_2O_8^{2-}$ for the reductants, with Cu^{3+} and $OH^{\cdot}$ being the most favourable, having the least electrostatic repulsion. For this situation k_{Cu} is defined as the zero-order rate constant divided by the $[Cu^{2+}]$ which is then all divided by $[S_2O_8^{2-}]$ ie. $(k_{obs}/[Cu^{2+}])/[S_2O_8^{2-}]$. Raw data are presented in Table A5.5.

Figure 5.4: Effect of $[Cu^{2+}]$ on the rate of oxidation of $[PtCl_4]^{2-}$ by peroxydisulfate (20 mM, 1.0 M HCl, 340 nm).



5.3.2 Hydrogen peroxide oxidations

The redox chemistry of hydrogen peroxide can be summarised by the following redox potentials:

$$H_2O_2 + 2H^+ + 2e \rightarrow 2H_2O \qquad E^o = 1.76\ V$$

$$O_2 + 2H^+ + 2e \rightarrow H_2O_2 \qquad E^o = 0.68\ V$$

$$HO_2^- + H_2O + 2e \rightarrow 3OH^- \qquad E^o = 0.87\ V$$

These show that H_2O_2 is a strong oxidising agent in either acidic or basic solution. It can behave as a reducing agent but only towards very strong oxidising agents eg. permanganate. Indeed, in this work the concentrations of the peroxide solutions were determined by titration with standardised potassium permanganate solution prior to each reaction.

Dilute (< 30 %) H_2O_2 solutions are widely used as oxidants. Its reactions are generally slower in acidic solution than in basic solution. The occurrence of the disproportionation of H_2O_2 to H_2O and O_2 means that solutions are unstable and therefore fresh solutions were prepared prior to each reaction.

Hydrogen peroxide is often used as an oxidising agent in the synthesis of platinum(IV) complexes [186]. It is a very effective oxidising agent and it produces the *trans* dihydroxo complex. If the reaction is performed in concentrated HCl, then generally the *trans* dichloro complex is formed. Although it is widely used in synthetic work there have been very few studies on the kinetics of oxidation of platinum(II) by H_2O_2 [105].

The platinum(II) complexes carboplatin, cisplatin, $[PtCl_2(chxn)]$, $[Pt(en)_2]^{2+}$, $[Pt(NH_3)_4]^{2+}$, $[Pt(ox)_2]^{2-}$, $[PtCl_4]^{2-}$, were oxidised by H_2O_2 in 1.0 M $HClO_4$ under

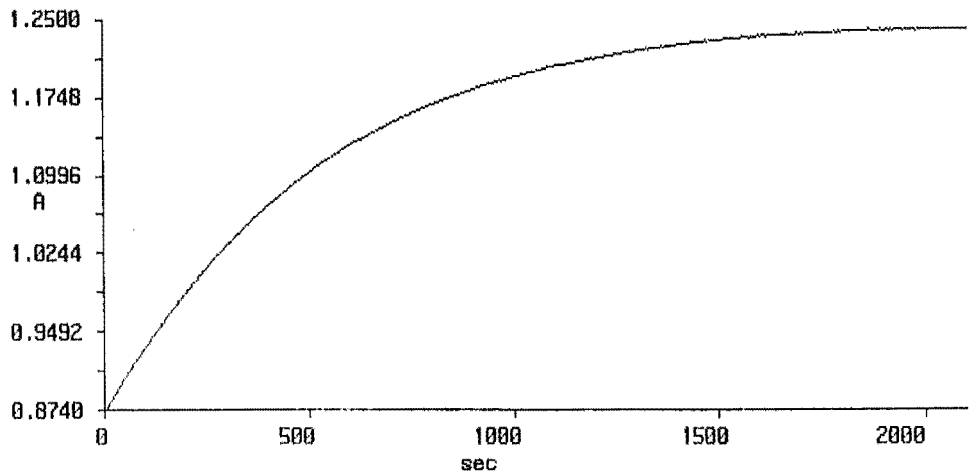
pseudo-first-order conditions ($[H_2O_2] \geq 10[Pt(II)]$). Kinetic data were obtained using the conventional spectrophotometric mixing technique described previously. In all cases, except for $[Pt(ox)_2]^{2-}$, the absorbance of the solution increased with time (Figure 5.5) without the generation of isosbestic points. For $[Pt(ox)_2]^{2-}$ a general decrease in absorbance was observed. Plots of k_{obs} *vs* $[H_2O_2]$ were linear with a zero intercept and the second-order rate constant, k_2, in the rate law (5.14) was calculated from the expression (5.15).

$$\text{rate} = k_2[Pt(II)][H_2O_2] \tag{5.14}$$

where $$k_2 = k_{obs}[H_2O_2]^{-1} \tag{5.15}$$

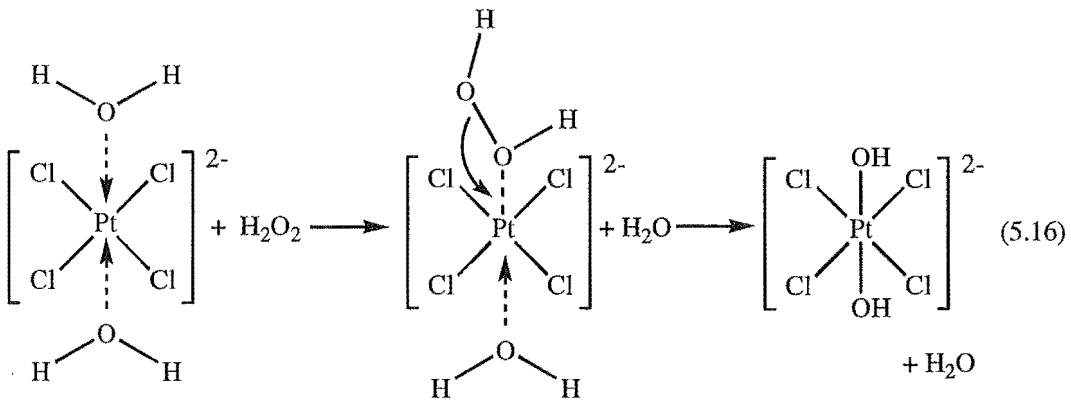
All k_2 data were used to estimate the activation parameters $\Delta S^{\#}$ and $\Delta H^{\#}$ (Table 5.2). Raw rate constant data are listed in Table A5.3.

Figure 5.5: Absorbance *vs* time scan for the oxidation of carboplatin by H_2O_2 (112.5 mM, 1.0 M $HClO_4$, 315 nm, 26 °C).



It is interesting to note that many reactions involving hydrogen peroxide in solution involve free radicals. This indicates that the oxidation of platinum(II) may

occur by two one-electron transfer steps with the production of the unstable platinum(III) intermediate. However, another possibility is the one-step two-electron transfer and this has been observed in some cases (ie. an encounter complex is formed between the platinum(II) complex and the H_2O_2, followed by a two-electron transfer step).



(5.16)

The product formed is exclusively *trans* and the oxidation occurs via a tetragonally distorted octahedral intermediate with the sixth coordination site associated with a water molecule from the solvent. Studies by Dunham *et al* [107] on the H_2O_2 oxidation of $[Pt(ox)_2]^{2-}$ using ^{195}Pt NMR techniques showed that the oxidation product is consistent with a platinum(IV) complex with six bonded oxygens. In this research the ^{195}Pt NMR was used to identify the product for both the $[Pt(ox)_2]^{2-}$ and $[PtCl_4]^{2-}$ complexes. A chemical shift of 2910 ppm was found for the oxidation product for $[Pt(ox)_2]^{2-}$ which agrees with the value quoted by Dunham *et al* (2873 ppm) [107]. A chemical shift of 1078 ppm was found for the oxidation product for $[PtCl_4]^{2-}$. This is the same value as that obtained for the peroxydisulfate oxidation of the same complex. Another peak was found in an aged solution at –284 ppm. This has been assigned as the platinum(IV) tetrachlorodiaqua complex.

Harrigan and Johnson [105] also studied the oxidation kinetics of $[Pt(NH_3)_4]^{2+}$

by H_2O_2 and their activation parameters are comparable to those obtained in this study (Table 5.2). They proposed a two-electron transfer step in their paper detailing peroxydisulfate and peroxide oxidations. Their reasoning was based on the observation that the peroxide oxidations were slower than for the peroxydisulfate reactions, whereas for other systems (where peroxide is known to oxidise in two one-electron steps) their rates are similar.

Table 5.2: Activation parameters for the oxidation of platinum(II) complexes by hydrogen peroxide (25 °C).

Complex	$10^3 k_2$[a] ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})
cis-$(NH_3)_2$	8.99	47 ± 2	-125 ± 6
carboplatin	18.2	52 ± 2	-102 ± 6
chxn	33.6	58 ± 3	-78 ± 9
$[Pt(en)_2]^{2+}$	3.70	70 ± 3	-58 ± 9
$[Pt(NH_3)_4]^{2+}$	3.15	66 ± 2	-71 ± 6
$[Pt(NH_3)_4]^{2+}$ [a]	0.46	58 ± 2	-117 ± 8
$[Pt(ox)_2]^{2-}$	155	53.5 ± 1.4	-81 ± 4
$[PtCl_4]^{2-}$	4.25	76 ± 3	-35 ± 9

[a] Ref. [105], I = 1.0 M.

5.3.3 Permanganate oxidation

Potassium permanganate is a very powerful oxidising agent and is also used in the synthesis of platinum(IV) complexes [116]. The rates of oxidation of carboplatin, $[Pt(NH_3)_4]^{2+}$, $[PtCl_4]^{2-}$ and $[Pt(en)_2]^{2+}$ were measured using an Applied Photo-Physics Biosequential SX-18MV Stopped-Flow Reaction Analyser (Table

5.3). Reactions were monitored at 520 nm where the large decrease in absorbance observed corrresponds to the loss of the characteristic purple permanganate colour.

The reaction was studied under pseudo-first-order conditions with [Pt(II)] ≥ 10[MnO_4^-] due to the high molar absorptivity of permanganate ($\varepsilon_{520} = 7500\ M^{-1}cm^{-1}$). Plots of k_{obs} *vs* [Pt(II)] were linear with zero intercept and the second-order rate constant, k_2, in rate law (5.17), was calculated from expression (5.18).

$$\text{rate} = k_2[\text{Pt(II)}][MnO_4^-] \qquad (5.17)$$

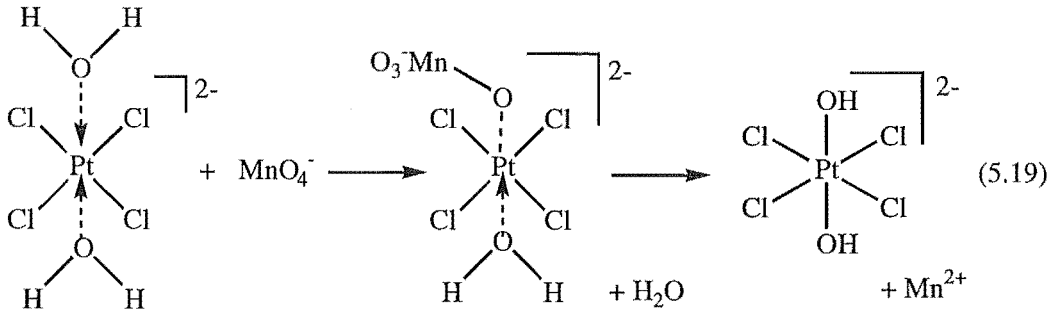
where $$k_2 = k_{obs}[\text{Pt(II)}]^{-1} \qquad (5.18)$$

The comparability between activation parameters (Tables 5.3) for all complexes indicates a similar mechanism occurs for neutral, anionic and cationic platinum(II) complexes. Raw data are listed in Table A5.4.

Table 5.3: Activation parameters for the oxidation of platinum(II) complexes by permanganate (0.1 M $HClO_4$, 25 °C).

Complex	$10^{-4}k_2$[a] ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})
carboplatin	10.5	16.9 ± 0.7	-92 ± 2
$[Pt(en)_2]^{2+}$	3.24	27.3 ± 0.6	-48 ± 2
$[Pt(NH_3)_4]^{2+}$	1.94	24.8 ± 0.7	-60 ± 2
$[PtCl_4]^{2-}$	3.44	29.5 ± 1.0	-59 ± 3

The proposed product is again the dihydroxyplatinum(IV) complex with a two-electron transfer (as for oxidation by H_2O_2).



(5.19)

Evidence for this product identification is that Zemskov *et al* were able to isolate *trans*-dihydroxotetrachloroplatinate (as the silver salt) after the oxidation of $[PtCl_4]^{2-}$ by permanganate [116]. ^{195}Pt NMR was not used to identify the reaction product due to the interference of Mn^{2+}.

5.3.4 Dichromate oxidation

Chromium(VI) has a wide and varied chemistry depending on pH and other factors. Many species are produced including the chromate ion (CrO_4^{2-}), and dichromate ($Cr_2O_7^{2-}$).

Potassium dichromate used in this study has a high molar absorbance in the UV ($\varepsilon_{350} = 2521\ M^{-1}cm^{-1}$). In order to monitor the reaction spectrophotometrically platinum(II) was in excess over dichromate, with $[Pt(II)] \geq 10[Cr_2O_7^{2-}]$. Repeat absorbance scans at fixed time interval showed a decrease in absorbance at 350 nm due to the loss of orange-red dichromate. This was observed for both complexes so all reactions were monitored at this wavelength.

The oxidation of $[PtCl_4]^{2-}$ was studied in 1.0M $HClO_4$. Plots of k_{obs} *vs* $[PtCl_4^{2-}]$ were linear with zero intercept (within experimental error) and data are presented in Table A5.6. It can be seen from the activation parameters (Table 5.4)

that the reaction has a low activation enthalpy. This manifests itself in the reactions not having a great dependence on temperature. For this reason the individual rate constants calculated were plotted against concentration and the least-squares fitted slopes used to calculate $\Delta H^{\#}$ and $\Delta S^{\#}$.

Dichromate was also used to oxidise carboplatin. As for $[PtCl_4]^{2-}$ the plots of k_{obs} *vs* [Pt(II)] were linear with zero intercept. The reaction was not greatly influenced by temperature thus the method above was used to calculate the activation parameters (Table 5.4).

Table 5.4: Activation parameters for the oxidation of platinum(II) by dichromate (1.0 M $HClO_4$, 25 °C).

Complex	k_2 ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})
$[PtCl_4]^{2-}$	14.91	17.3 ± 0.7	-164 ± 2
carboplatin	4.37	32.0 ± 1	-125 ± 3

The most probable mechanism for dichromate oxidation will involve the formation of an encounter complex followed by electron transfer giving the dihydroxo platinum(II) product. Before oxidation platinum(II) has two spare coordination sites. Upon oxidation one of these will be coordinated to an oxygen originating from the dichromate and the other will coordinate a solvent molecule. It is not possible to verify the product using NMR due to the paramagnetic nature of the Cr^{3+} oxidation product.

$$[PtCl_4]^{2-} + Cr_2O_7^{2-} \rightarrow [Cr_2O_7 \cdots PtCl_4]^{2-} \rightarrow [Pt(OH)_2Cl_4]^{2-} + Cr^{3+} \qquad (5.20)$$

A small negative salt effect was observed when the $[ClO_4^-]$ was varied and

the rate of oxidation increased as $[H^+]$ increased.

5.3.5 Correlation with reduction potential

It was thought that the order of reactivity of the three oxidising agents might mirror their respective reduction potentials. As seen in Table 5.5 this does not appear to be the case.

Table 5.5: Comparison between rate of reaction and reduction potential for the oxidation of carboplatin.

k_{ox} (25 °C, $M^{-1}s^{-1}$)	Reduction potential [123]	
20.5×10^{-2} [a]	$S_2O_8^{2-} + 2e \rightarrow 2SO_4^{2-}$	1.96 V
1.82×10^{-3} [a]	$H_2O_2 + 2H^+ + 2e \rightarrow H_2O$	1.763 V
10.5×10^{4} [b]	$MnO_4^- + 8H^+ + 5e \rightarrow Mn^{2+} + 4H_2O$	1.51 V
4.37	$Cr_2O_7^{2-} + 14H^+ + 6e \rightarrow 2Cr^{3+} + 7H_2O$	1.38 V

[a] 1.0 M $HClO_4$. [b] 0.1 M $HClO_4$.

There are no clear correlations between the oxidants but once again, it is difficult to compare the systems due to the variable number of electrons transferred.

5.4 CONCLUSIONS

The oxidations of platinum(II) complexes by hydrogen peroxide, potassium permanganate and potassium dichromate appear to proceed via direct two-electron transfers. However, the oxidation by peroxydisulfate results in two different processes. For neutral and positively charged complexes (eg. carboplatin and $[Pt(en)_2]^{2+}$) the mechanism involves one two-electron transfer step as above, but for

the negatively charged complexes (eg. $[PtCl_4]^{2-}$) a radical mechanism with two one-electron transfer steps is most likely.

The mechanism for the one-step process probably involves the formation of an 'encounter' complex between the oxidising agent and the platinum(II) complex. Once formed, the two-electron transfer can take place via O-atom transfer and the encounter complex breaks into the appropriate products. This model would predict one O-atom in the dihydroxo product to come from the oxidising agent and the other from the solvent water (Equations (5.16) and (5.19)). Indeed, Dunham *et al* [106] have used O isotopic labelling studies to show that the mechanism begins with the addition of $H_2{}^{16}O_2$ to a vacant coordination site. An $H_2{}^{16}O$ or $H_2{}^{18}O$ from the solvent fills the other vacant coordination site. The above scenario is less likely for the reaction between peroxydisulfate and negatively charged complexes due to electrostatic repulsion, and a radical mechanism dominates.

The suggested mechanisms for all oxidants are consistent with those expected on the basis of the thermal activation parameters for both the oxidation and reduction reactions (Chapter 4). The large negative activation entropy values are indicative of an associative-interchange mechanism (see Chapter 2, Section 2.7). This is in accord with the proposed mechanism involving O-atom transfer.

CHAPTER 6

BASE HYDROLYSIS OF PLATINUM(IV)

6.1 INTRODUCTION

The base hydrolysis of inert coordination compounds has been extensively studied for cobalt(III), rhodium(III), chromium(III), iridium(III) and platinum(II) (eg. Equation (6.1)) [188].

$$[MCl(NH_3)_5]^{2+} + OH^- \rightarrow [M(OH)(NH_3)_5]^{2+} + Cl^- \qquad (6.1)$$

For the chloroamminecobalt(III) system a first-order dependence in [OH^-] was found.

$$-d[Co(III)]/dt = k_{OH}[Co(III)][OH^-] \qquad (6.2)$$

The kinetics of this process were explained in terms of an acid-base pre-equilibrium, followed by dissociation of the conjugate base of the complex (S_N1CB mechanism) [189]. This is now the accepted mechanism for base hydrolysis [190].

$$[Co(NH_3)_5Cl]^{2+} + OH^- \rightleftharpoons [Co(NH_3)_4(NH_2)Cl]^+ + H_2O \qquad (6.3)$$

$$[Co(NH_3)_4(NH_2)Cl]^+ \longrightarrow [Co(NH_3)_4(NH_2)]^{2+} + Cl^- \qquad (6.4)$$

$$[Co(NH_3)_4(NH_2)]^{2+} + H_2O \longrightarrow [Co(NH_3)_5(OH)]^{2+} \qquad (6.5)$$

Compared with all other nucleophiles the hydroxide ion falls into a special category. Even low concentrations of OH^- can affect the release of halide ions (or other labile ligands) from octahedral metal centres. Other nuclephiles eg. N_3^-, NO_2^-

have no effect on reaction rates as it is thought that the complexes undergo an aquation reaction prior to substitution. This is one piece of evidence as to why an S_N1CB mechanism is likely for base hydrolysis.

The S_N1CB mechanism was proposed by Garrick [191] who based his ideas on work by Brønsted and Erlenmeyer [192]. S_N1CB stands for substitution, nucleophilic, unimolecular, conjugate base. It was first proposed for the base hydrolysis of cobalt complexes (as in equations (6.3) - (6.5)). Equation (6.3) must occur but only to a small extent otherwise all the complex will be converted to the conjugate base form. Then, as the concentration of hydroxide increases there will be no further change in rate ie. saturation kinetics are observed.

$$k_{obs} = k_2K_1[Co(III)][OH^-]/(1 + K_1[OH^-]) \qquad (6.6)$$

Another possible reason for saturation kinetics is ion-pair formation. Saturation kinetics have previously only been observed by Chan [193].

The S_N1CB mechanism is essentially a dissociative process stereochemically, indicating a trigonal bipyramidal intermediate structure for both *cis* and *trans* isomers.

For several metal ammine complexes (M = Co, Cr, Ru) the base hydrolysis reactions have been found to be first-order in hydroxide and first-order in complex (Equation (6.2)). Platinum(IV) complexes are known to be very inert and the few earlier studies of their base hydrolysis have given ambiguous results [188, 194 - 196] with variable reaction orders. It was thus decided to reinvestigate the base hydrolysis of selected platinum(IV) complexes. One requirement for base hydrolysis is that there must be a moderately acidic proton with which to form the conjugate base and the complexes chosen for this study all meet this requirement.

The earlier work on base hydrolysis came from two research groups; Grinberg in Russia and Johnson in the USA.

Grinberg found that the rate for the substitution of the pentaamminechloro-platinum(IV) complex ($[PtCl(NH_3)_5]^{3+}$) was first order in both hydroxide and platinum(IV) [195] as expected for an S_N1CB mechanism. In his paper in 1964 [187] he studied the aquation of the *cis*- and *trans*-$[PtCl_4(NH_3)_2]$ isomers. He measured this by two methods - titration of the aquation products with 0.01 N NaOH and by measuring the rate of change in electrical conductivity and pH. He found that the *trans* complex aquated faster than the *cis* complex (2×10^{-5} s^{-1} *vs* 6.1×10^{-6} s^{-1}, $[OH^-] = 0.25$ mM, T = 50 °C) and he attributed this to the *trans* complex having two Cl-Pt-Cl axes. In his work in 1966 [194] when studying the base hydrolysis of these complexes he found that the rate of reaction was proportional to $[OH^-]$ for the *cis* complex giving an S_N1CB mechanism, but $[OH^-]^{0.35}$ for the *trans* complex with a complex mechanism.

Work by Johnson and Basolo [188] found that the chloroammineplatinum(IV) complexes studied released chloride by at least three different processes. One reaction involved the simple replacement of coordinated chloride by hydroxide ($[PtCl(NH_3)_5]^{3+}$ and *cis*-$[PtCl_2(NH_3)_4]^{2+}$). For all *cis* complexes there were no platinum(II) products detected and the rate of hydrolysis was not affected by addition of $[Pt(NH_3)_4]^{2+}$. However, for all *trans* complexes some reduction of platinum(IV) occurred. For *trans*-$[PtCl_3(NH_3)_3]^+$ and *trans*-$[PtCl_2(NH_3)_4]^{2+}$ the reduction pathway was thought to be responsible for 10 % of the chloride lost. *Trans*-$[PtCl_2(en)_2]^{2+}$ was a more extreme case with up to 90 % of the Cl^- being lost through a reduction pathway.

These very early studies leave a unclear picture of base hydrolysis and it was hoped reinvestigation using spectrophotometric techniques would clarify some mechanistic details.

6.2 EXPERIMENTAL

6.2.1 Materials

The platinum(IV) complexes *cis*-$[PtCl_4(NH_3)_2]$ and *trans*-$[PtCl_4(NH_3)_2]$ were commercially available (Strem) and used as supplied. *Trans*-$[PtCl_2(en)_2](ZnCl_4)$ and *trans*-$[PtCl_2(NH_3)_2]Cl_2$ were synthesised as described below. $[PtCl(NH_3)_5]Cl_3$ was prepared by Professor D.A. House. Sodium hydroxide and sodium perchlorate were of the best reagent grade available.

All complexes except c*is*- and *trans*-$[PtCl_4(NH_3)_2]$ were studied over a hydroxide range of 0.2 - 1.0 M with ionic strength maintained at 1.0 M by addition of sodium perchlorate. NaOH (6 mL) was heated to the desired temperature in the 4 cm pathlength cell. Approximately 1 mg of complex was added. In all cases (except *cis*-$[PtCl_4(NH_3)_2]$) the complex dissolved upon gentle shaking and the cell was then placed in the electrically heated cell block unit (as described in Chapter 2). This procedure was used for *trans*-$[PtCl_4(NH_3)_2]$ but with hydroxide concentrations of 10 - 100 mM. For *cis*-$[PtCl_4(NH_3)_2]$ a stock solution was prepared (7.4 mg/20 mL, 9.97 x 10^{-4} M, in water). 3 mL of the platinum(IV) solution and 3 mL NaOH were mixed and then transferred to the 4 cm pathlength cell as for the other complexes. For these reactions the final concentrations of NaOH ranged from 15.0 - 45.0 mM.

For all complexes, repeat scans (Figures 6.1 and 6.3) showed a decrease in absorbance at $\lambda < 400$ nm without the generation of isosbestic points. The reactions

were then monitored at fixed wavelength (*trans*-$[PtCl_2(NH_3)_4]^{2+}$ 340 nm, *trans*-$[PtCl_2(en)_2]^{2+}$ 350 nm, *cis*-$[PtCl_4(NH_3)_2]$ 330 nm, *trans*-$[PtCl_4(NH_3)_2]$ 330 nm and $[PtCl(NH_3)_5]^{3+}$ 310 nm) for at least 6 - 8 half-lives and the observed rate constant k_{obs}, calculated from the usual absorbance *vs* time expression (see Chapter 2).

6.2.2 Synthesis of *trans*-$[Pt^{IV}Cl_2(NH_3)_4]Cl_2$

$[Pt^{II}(NH_3)_4]Cl_2$ (250 mg) was dissolved in 5 mL H_2O. 5 mL concentrated HCl was added and the mixture stirred. 2 mL H_2O_2 (30 %) was added and a pale yellow solid formed immediately. This was filtered using a sintered glass crucible giving 269 mg (89.8 %) of *trans*-$[Pt^{IV}Cl_2(NH_3)_4]Cl_2$.

6.2.3 Synthesis of *trans*-$[Pt^{IV}Cl_2(en)_2](ZnCl_4)$

$[Pt^{II}(en)_2]Cl_2$ (250 mg) was dissolved in 5 mL H_2O. 5 mL concentrated HCl was added and the mixture stirred. 2 mL H_2O_2 (30 %) was added. The solution changed from colourless to pale yellow but no formation of solid occurred. After three days the solution was heated on a steam bath to 40 °C and 0.5 g $ZnCl_2$ added. A white crystalline solid formed immediately. This was filtered using a sintered glass crucible giving 340 mg (98.9 %) of *trans*-$[Pt^{IV}Cl_2(en)_2](ZnCl_4)$. An X-ray crystal structure of this complex confirmed the expected structure and selected crystal data are presented in Table A6.3.

6.3 RESULTS AND DISCUSSION

6.3.1 $[PtCl(NH_3)_5]^{3+}$

With just one chloride ion to be substituted by hydroxide it was expected that the reaction would obey simple first-order kinetics. Repeat scans (Figure 6.1)

showed a decrease in absorbance without generation of isosbestic points. Plots of k_{obs} *vs* [OH^-] (Figure 6.2) were linear with zero-intercept giving rise to the expected rate law

$$\text{rate} = k_{OH}[\text{Pt(IV)}][OH^-] \qquad (6.7)$$

which is second-order overall. The mechanism in this reaction will involve a simple replacement of coordinated chloride by hydroxide. This was also observed in the early work by Johnson *et al* [188]. Raw data are presented in Table A6.1.

Figure 6.1: Repeat scans (180 s time interval) showing a decrease in absorbance for the base hydrolysis of $[PtCl(NH_3)_5]^{3+}$ (0.1 M NaOH, 32.2 °C).

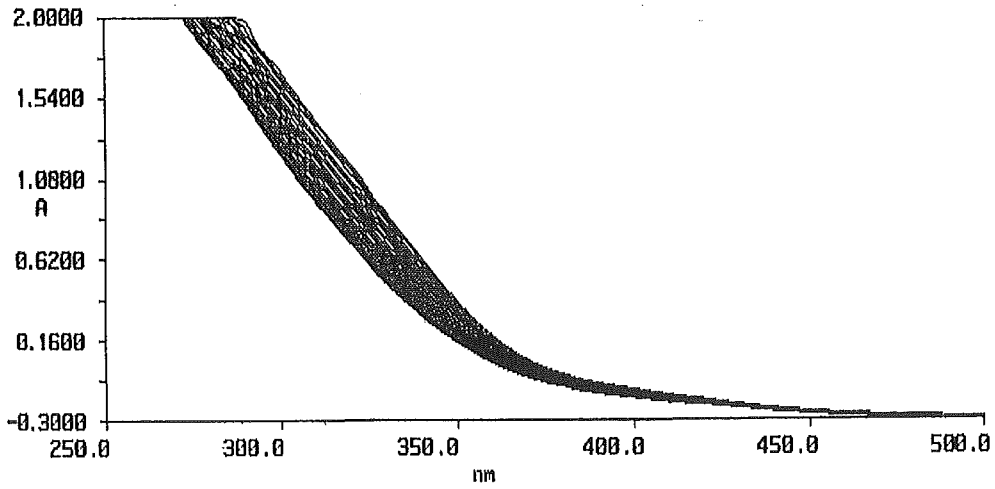
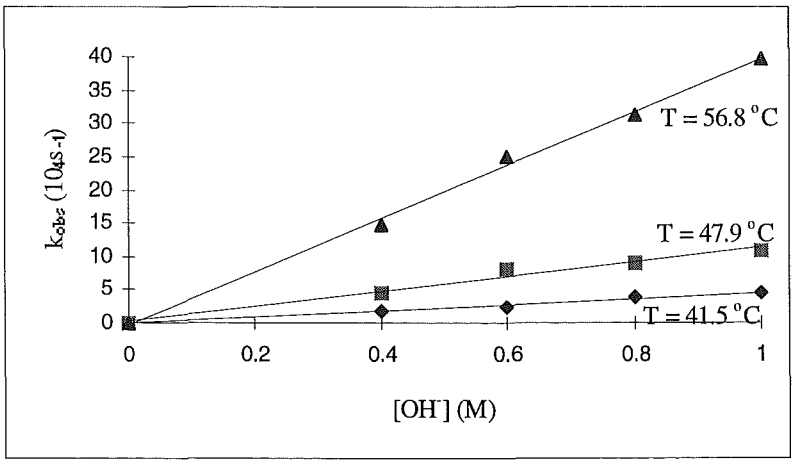


Figure 6.2: Linear plot of [OH^-] *vs* k_{obs} for the base hydrolysis of $[PtCl(NH_3)_5]^{3+}$ (I = 1.0 M).



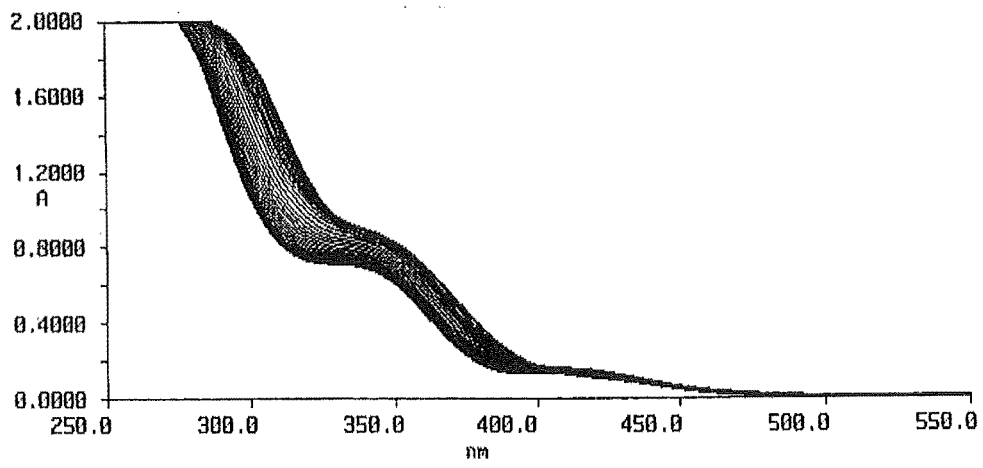
6.3.2 *trans*-$[PtCl_2(en)_2]^{2+}$ and *trans*-$[PtCl_2(NH_3)_4]^{2+}$

Absorbance *vs* time scans repeated at 3 minute intervals showed one reaction for both complexes, which was assumed to be the removal of the first chloride ligand. Free chloride ion titrations [144a] confirmed this assumption, with only one free chloride ion detected. Due to the *trans* effect, where OH^- has less of an effect than Cl^-, substitution of the second chloride ion is expected to be slow. This was qualitatively observed with further small changes in absorbance occurring at the end of the initial reaction. Plots of k_{obs} *vs* $[OH^-]$ were linear with zero intercept (within experimental error). The second order rate constant k_{OH} was calculated from the expression $k_{OH} = k_{obs}[OH^-]^{-1}$. Activation parameters are listed in Table 6.1 and raw data in Table A6.1.

6.3.3 *cis*- and *trans*-$[PtCl_4(NH_3)_2]$

Repeat absorbance *vs* time scans showed a decrease in absorbance (Figure 6.3). However when observing this at single wavelengths two reactions were seen. Figure 6.3 shows that the process is not "clean".

Figure 6.3: Repeated spectra (180 s time interval) showing the 'unclean' repeat absorbance scans for the base hydrolysis of *cis*-$[PtCl_4(NH_3)_2]$ (0.1 M NaOH, 44.6 °C).

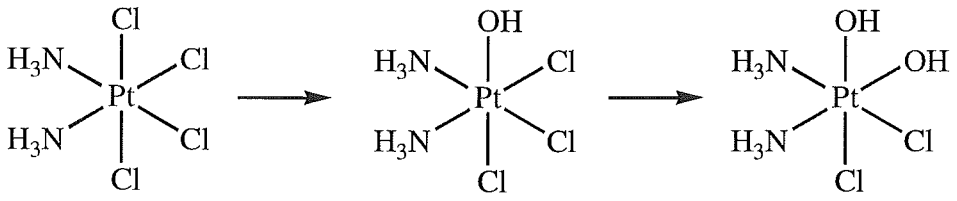


The first reaction resulted in a small increase in absorbance, followed by a slower decrease for the second. Attempts to monitor the first reaction were unsuccessful due to the small absorbance change, ie. scans were very noisy, and thus only the second reaction was monitored. It is thought that this second reaction will be the substitution of a second chloride ion. No other subsequent reactions were observed. Free chloride ion titrations [144a] on a freshly prepared solution ($[OH^-]$ = 0.1 M) indicated one chloride ion released, but a solution subjected to reaction conditions (ie. one hour reaction time at 80 °C) showed two chloride ions released. These results are in agreement with the spectrophotometric results ie. one chloride substituted rapidly and the next more slowly. The slow reaction is that measured.

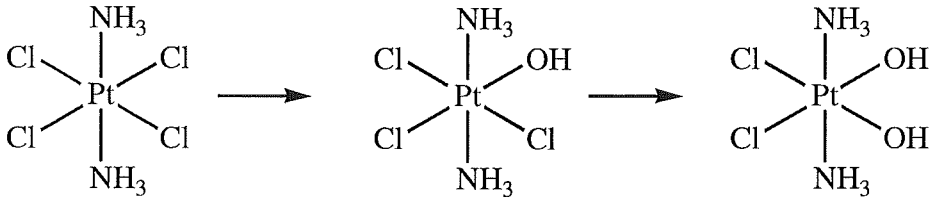
When *cis*- and *trans*-$[PtCl_4(NH_3)_2]$ complexes were studied in the $[OH^-]$ range 0.2 - 1.0 M, plots of k_{obs} *vs* $[OH^-]$ were non-linear and showed saturation kinetics. It was decided that other processes were swamping the reaction under study eg. possibly other chloride ions being replaced by the hydroxo ligand. Another explanation for the saturation kinetics is based on the conjugate base mechanism as discussed earlier (Section 6.1). This mechanism suggests that at a sufficiently high concentration of hydroxide, a stage could be reached where all the original complex has been converted into the conjugate base form so that further increases in hydroxide concentration have no effect on the rate. Reactions were therefore studied at a lower hydroxide concentration over which plots of k_{obs} *vs* $[OH^-]$ were linear with zero intercept. Raw data are tabulated in Table A6.2.

Under identical conditions the *cis* isomer reacts slightly slower than the *trans* isomer. For the second chloride release, the *trans* complex still has one Cl-Pt-Cl axis while the *cis* isomer has none and therefore it is expected that the *trans* isomer will react faster. As NH_3 and NH_2^- have stronger *trans* effects than OH, it is likely that

the second chloride (on the *cis* isomer) replaced will be *trans* to a NH_3.



A similar diagram for *trans* complexes is:



Ionic strength effects were measured for *cis*-$[PtCl_4(NH_3)_2]$ and $[PtCl(NH_3)_5]^{3+}$. No effect was found for the neutral complex, but a negative salt effect was observed for $[PtCl(NH_3)_5]^{3+}$. This is expected for a reaction between ions of different charges.

6.3.4 Mechanistic interpretation

The most likely mechanism for the base hydrolysis of platinum(IV) complexes is an S_N1CB type mechanism (Equations (6.8) - (6.10)). This would involve the initial formation of a conjugate base species before hydrolysis occurs. Evidence for the formation of a conjugate base species comes from the absorbance spectra of the platinum(IV) complexes. When in acidic or neutral media the absorbance spectra are the same, but when in base the spectrum changes. This alone does not necessarily mean a conjugate base is formed, but the only other explanation is ion-pair formation. This can be discounted as the formation of ion-pairs would give rise to

saturation kinetics [193].

$$[PtCl(NH_3)_5]^{3+} + OH^- \rightleftharpoons [PtCl(NH_2)(NH_3)_4]^{2+} + H_2O \quad (6.8)$$

$$[PtCl(NH_2)(NH_3)_4]^{2+} \longrightarrow [Pt(NH_2)(NH_3)_4]^{3+} + Cl^- \quad (6.9)$$

$$[Pt(NH_2)(NH_3)_4]^{3+} + H_2O \longrightarrow [PtCl(OH)(NH_3)_5]^{3+} \quad (6.10)$$

Another mechanism may involve a preliminary aquation step. Studies on the complex hydrolysis in water and acid showed that this pathway is not likely due to the extreme slowness of the reaction and as the diammines are weakly acidic [190], the S_N1CB mechanism discussed above may be the most applicable.

Further to this, qualitative experiments found that acid hydrolysis for these platinum(IV) complexes is very slow (no reaction was observed over 10 hours at 40 °C). This is in contrast to platinum(II) complexes where base hydrolysis is much slower than acid hydrolysis. An explanation for the slowness of platinum(II) base hydrolysis may be due to the possible stabilisation of the transition state due to hydrogen bonding between an ammine ligand and the hydroxo oxygen. However, as platinum(II) complexes base hydrolyse by a completely different mechanism [51] it is difficult to compare the two different oxidation states.

Some of the earlier studies have indicated that the *trans* platinum(IV) complexes are partially reduced during the base hydrolysis process [188]. To investigate this a ^{195}Pt NMR spectrum of the final reaction mixture was run for *trans*-$[PtCl_4(NH_3)_2]$. No peaks were observed at -2854 ppm, the chemical shift for the most likely platinum(II) reduction product $[Pt(NH_3)_4]^{2+}$ [196]. From this it is assumed that extensive reduction is not occurring.

Table 6.1: Activation parameters for the base hydrolysis of platinum(IV) complexes (25 °C).

Complex	k_{OH} ($10^4 M^{-1}s^{-1}$)	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})
$[PtCl(NH_3)_5]^{3+}$ [a]	0.308	123 ± 2	80.0 ± 6
trans-$[PtCl_2(NH_3)_4]^{2+}$ [a]	0.327	84.6 ± 3	30 ± 9
trans-$[PtCl_2(en)_2]^{2+}$ [a]	1.12	102 ± 4	21.6 ± 12
cis-$[PtCl_3(OH)(NH_3)_2]$ [b]	6.07	108 ± 5	55.4 ± 15
trans-$[PtCl_3(OH)(NH_3)_2]$ [b]	7.41	101 ± 5	35 ± 15

[a] I = 1.0 M. [b] I = 0.1 M

Consideration of the data in Table 6.1 show that platinum(IV) complexes undergo base hydrolysis at a slow rate. The positive activation entropy for all five complexes is another indication of an S_N1CB mechanism. The large positive activation entropy value is due to charge neutralisation. If a direct displacement reaction were to take place a negative activation entropy would be expected [197]. The first step in this type of mechanistic scheme requires the formation of a conjugate base. Stereochemical results support the conclusion that formation of an amido group *cis* rather *trans* to the leaving group leads to the trigonal bipyramidal intermediate [198]. It is thought that this intermediate is stabilised by π donating groups. This stabilistion is not possible for a *trans* amido group [197].

Table 6.2: Comparison of rate parameters for the base hydrolysis of $[MCl(NH_3)_5]^{n+}$ complexes.[a]

M	k_{OH} (25 °C) ($M^{-1}s^{-1}$)	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})
Cr(III)	4.9	112	143
Co(III)	1.58	114	140
Ru(III)	1.85×10^{-3}	109	69
Rh(III)	4.1×10^{-4}	117	82
Pt(IV)	3.1×10^{-5}	123	80.0

[a] Ref. [189].

The data in Table 6.2 show that the platinum(IV) complex hydrolyses slower than the other metal complexes. All five metal centres have similar activation enthalpies and large positive entropies for their base hydrolysis. The latter suggests that they all hydrolyse by the same mechanistic process - S_N1CB.

6.3.5 X-ray crystal structure of *trans*-$[PtCl_2(en)_2](ZnCl_4)$

During the synthesis of *trans*-$[PtCl_2(en)_2](ZnCl_4)$ white crystals suitable for an X-ray crystallographic study formed (Figure 6.4). The structure was determined by Professor Ward Robinson in the same way as the structures discussed in Chapter 3. The average Pt(IV)-N and Pt(IV)-Cl bond lengths were 2.05 Å and 2.30 Å respectively. The torsion angles indicate that the en rings have a λδ configuration. Further details are given in Table A6.3.

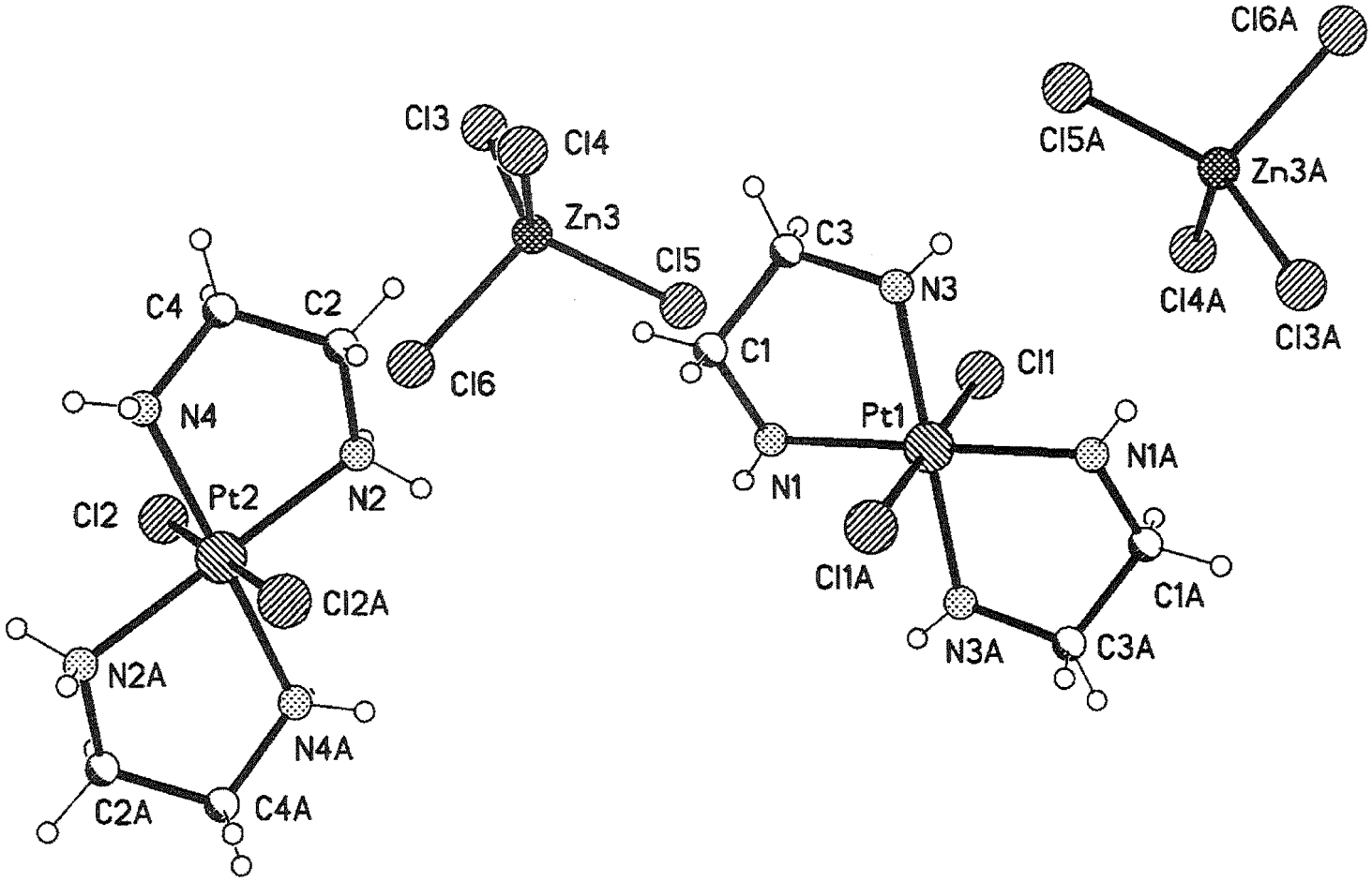


Figure 6.4: X-ray crystal structure of *trans*-$[PtCl_2(en)_2](ZnCl_4)$.

6.4 CONCLUSIONS

To date there have been very few studies on the base hydrolysis of platinum(IV) complexes – the last being in the 1960's. Because of this, a study was undertaken to reinvestigate the base hydrolysis of platinum(IV)-amine complexes.

The base hydrolysis of five chloroammineplatinum(IV) complexes has been studied over a range of hydroxide ion concentrations. Results indicate an S_N1CB mechanism as found for other octahedral complexes eg. cobalt(III). The mechanism was assigned by considering the activation entropy and the absorbance spectra. A mechanism of this type requires the initial formation of a conjugate base species which is only possible if there is an acidic proton in the complex.

Therefore, from the work in this chapter it seems likely that an S_N1CB mechanism occurs for the base hydrolysis of platinum(IV) chloroammine complexes.

CHAPTER 7

CONCLUSIONS

The introduction to this thesis gave a summary of the discovery, use, DNA interactions, redox and hydrolysis chemistry of cisplatin. The fact that cisplatin is such a successful anti-cancer drug, with a cure rate of over 90 % for testicular cancer, has meant that many research groups have focussed their efforts into probing the chemistry and biochemistry of this, and other related complexes. Expected outcomes from this large body of research have been to improve the efficiency of cisplatin treatment protocols and to find more successful platinum-based drugs. In order to achieve these outcomes it is necessary to have an understanding of the fundamental chemistry of cisplatin. The aim of this thesis was therefore to expand the simple chemical knowledge about cisplatin, carboplatin and related platinum amine complexes (for both +II and +IV oxidation states).

The work presented in this thesis further investigates some of the simple chemistry of cisplatin and other related complexes. This includes the platinum(II) complexes and platinum(IV) complexes which have been shown to be effective anti-tumour agents. Although there has been a lot of research into the chemistry of cisplatin, it is necessary to extend this for chemically related (but not necessarily biologically active) platinum(II) complexes in order to better understand why cisplatin is a most effective anti-cancer drug. It is also necessary to investigate the chemistry of the newer platinum(IV)-based complexes (eg. JM-216). This will provide information about their chemistry from which it is hoped a better understanding of the mechanism of action *in vivo* will arise.

Chapter 3 of this work describes the chloride and bromide anation reactions for a range of platinum(II) amine complexes in 1.0 M $HClO_4$ (Equations (3.1) and (3.2)). It is important to understand the hydrolysis/anation chemistry of these complexes due to the suspected *in vivo* mode of action of cisplatin. The chloride anation of the diaqua (*cis*-$[Pt(N)_2(OH_2)_2]^{2+}$) complexes (k_{-2}, equation (3.2)) was initially investigated. The rate of chloride anation of these complexes was 10 – 15 times faster than the monoaqua anation. This ratio increased to 94 for transplatin due to a decrease in activation enthalpy. All complexes (except transplatin) have similar activation parameters and an associative-interchange mechanism for the anation process is most likely. The reaction showed a negative salt effect as expected for reactants of differing charge.

The equilibrium constant, K_2, associated with the anation/hydrolysis of the diaqua was determined by Hg^{2+} titration. Values for k_2 ($k_2 = K_2k_{-2}$) calculated were of similar magnitude ($\approx 10^{-5}$ s^{-1}) to previously determined values for k_1. Consideration of the equilibrium constants K_1 and K_2 indicate that the second hydrolysis reaction (ie. K_2) is less favourable, and in the biological situation, cisplatin is unlikely to hydrolyse in any great amount to the diaqua complex.

In acid solution, cisplatin hydrolyses more slowly than any of the other dichloro-platinum(II) complexes studied in this work. This may be significant in terms of its anti-tumour activity. When crossing from the plasma to the cell, the intact cisplatin undergoes the first hydrolysis reaction (Equation (3.1)) due to a change in the chloride ion concentration gradient. The long aquation time and unfavourable equilibrium for the second hydrolysis means that the drug, once in the biologically active monoaqua form, is more likely to react with biomolecules (eg. DNA) than form the diaqua species. The inertness of cisplatin both to anation and

aquation, compared to the other non-biologically active platinum amine complexes, may be one reason why it is such an effective anti-tumour drug.

The bromide ion anation of platinum(II) amine complexes was also investigated. In these cases values for k_1, k_{-1}, and k_{-2} were measured. Stopped-flow techniques were necessary to determine k_{-2} due to the rapidity of the reaction. The bromide anation of the bromoaqua was 2 – 5 times faster than the equivalent chloride anation of the chloroaqua with relatively constant activation enthalpy values. A similar trend was seen with the bromide anation of the diaqua, which was 5 fold greater than the analogous chloride anation. Again, for all complexes the activation entropy was negative, indicating the likelihood of an associative-interchange mechanism - the most common mechanism for substitution reactions of square-planar complexes. The effect of the non-replaced amine ligands on the order of reaction rate (for k_{-2}) was identical for both chloride and bromide ion anation, probably due to simple steric effects.

A further aspect to this work was a high-pressure stopped-flow study. The sign and magnitude of activation volumes can also be used (along with activation entropy) as an indicator of reaction mechanism. The technique used allowed calculation of the activation volume for selected reactions. The small, negative values calculated for $\Delta V^{\#}$ are indicative of an associative-interchange mechanism as predicted by the activation entropy values.

Single crystal X-ray studies of the products resulting from the evaporation of residues from the bromide ion anation studies, showed that tetrabromoplatinum(IV) complexes were produced. The platinum(II) residues were oxidised, either atmospherically or by bromine produced in the residue containers, to platinum(IV) tetrabromodiamine complexes. A ^{195}Pt NMR investigation on these and chxn and

Me_2tn crystals (unsuitable for X-ray study) seemed to indicate a similar structure, with all four complexes having similar chemical shifts.

It is often discussed why cisplatin shows anti-tumour activity whereas its isomeric *trans* form is inactive. In fact, transplatin is active, but a higher dosage is required which can exacerbate the undesirable side-effects associated with cisplatin. The basis for the difference can be attributed to the difference in reactivity – the diaqua for of transplatin anates faster than the diaqua form of cisplatin. The *trans* effect can be used to explain this feature as Cl^- has a stronger effect than water, and thus hydrolysis *trans* to a chloride (ie. transplatin) is more likely. NH_3 is also involved in directing, but to a lesser extent than Cl^-. However, the aquation of transplatin is slower than that for cisplatin which is in disagreement with the *trans* effect.

Thus Chapter 3 extends the available knowledge on the simple reaction chemistry of cisplatin and other related platinum amine complexes. This knowledge may prove useful in aiding the development of new, improved anti-tumour platinum drugs.

The more recent development of platinum(IV) based anti-tumour drugs has led to an increase of interest in the redox chemistry of platinum(II) and platinum(IV). The platinum(IV) drugs are thought to be reduced *in vivo* to the corresponding platinum(II) complex and biological studies seem to confirm this mechanism. Information on the rate of reduction of platinum(IV) model complexes is important for the development of new drugs and treatment protocols eg. the activity of a drug may be enhanced by co-administration of a reducing agent.

Chapter 4 studied the reduction of three model platinum(IV) complexes with ascorbic acid, Sn(II), Fe(II), $S_2O_3^{2-}$ and hydroxylamine. Reductions by Sn(II) and

Fe(II) appear to proceed by a chloride bridged mechanism while the other reductants may react via the formation of an outer-sphere encounter complex prior to electron transfer.

The most effective (ie. fastest) reductant was ascorbic acid, the biological reducing agent. It seems likely, considering work by others [89 - 90], that there are many possible *in vivo* reducing agents that can reduce platinum(IV) anti-cancer drugs. Of these, it is expected that the sulfur containing complexes eg. glutathione and methionine will be the most prevalent reductants, but ascorbic acid may also play an important role. If the complex is reduced too quickly there may be an increase in side-effects due to extraneous reactions between the platinum(II) complex and other biological nucleophiles. In such a situation it is necessary to have an effective, but not too powerful, reducing agent. In order to gain more insight into these reactions they must be studied under strict biological conditions ie. pH = 7.4.

The other reductants, although not biologically relevant, were selected to provide mechanistic comparisons. Of all chosen, Fe(II) is the only non-complementary reductant. The mechanism for this, though, is similar to that proposed for Sn(II), where a chloride-bridged structure is formed prior to electron transfer. Thiosulfate and hydroxylamine reductions appear to involve the formation of an electrostatic encounter complex before electron transfer. Ascorbic acid reductions may be more dependent on electrostatics. The large difference in activation parameters between the negatively charged $[PtCl_6]^{2-}$ and the neutral *cis*- and *trans*-$[PtCl_4(NH_3)_2]$ may be attributed to electrostatic effects. At pH 4 (ie. reaction pH), the main reactant is likely to be HA^-. The proposed mechanism involves the formation of an ascorbate radical anion and the formation of transient platinum(III).

The main route for the preparation of platinum(IV) complexes is via the oxidation of platinum(II) compounds. Very few studies have measured the kinetics of oxidation of platinum(II) and thus it was decided to study the oxidation kinetics of platinum(II) using hydrogen peroxide, peroxydisulfate, permanganate and dichromate as oxidants. For peroxide, permanganate and dichromate, reactions may proceed by one two-electron transfer involving an oxygen-transfer pathway. The most probable final product for all oxidants will be the *trans*-dihydroxo complex. It is likely that one oxygen will come from the oxidant and the other from the solvent. ^{195}Pt NMR has provided evidence for this when H_2O_2 is the oxidising agent, however due to the production of paramagnetic Mn^{2+} and Cr^{3+} NMR could not be used for permanganate and dichromate.

The kinetic pattern observed in peroxydisulfate oxidations is highly dependent on the charge of the platinum(II) complex. Positively charged and neutral complexes are oxidised in a two-electron transfer pathway, similar to the other oxidants described above. Negatively charged complexes, eg. $[PtCl_4]^{2-}$, proceed by a one-electron transfer mechanism involving the production of platinum(III) and $SO_4^{\cdot-}$ radicals. The rate law for these oxidations is independent of platinum concentration and thus the reaction is zero-order in platinum(II). This completely alters the absorbance *vs* time spectra, giving a linear increase in absorbance with time before a sharp levelling off at the end of the reaction. Mechanisms of this type are not common, but have been previously observed for the acetone/iodine reactions [122].

The penultimate chapter in this thesis describes a study on the base hydrolysis of platinum(IV) chloroammine complexes. $[PtCl(NH_3)_5]^{3+}$, *trans*-$[PtCl_2(en)_2]^{2+}$ and *trans*-$[PtCl_2(NH_3)_4]^{2+}$ hydrolyse in basic solution releasing just one chloride ion.

The neutral complexes *cis*- and *trans*-$[PtCl_4(NH_3)_2]$ release two chloride ions under the selected reaction conditions and for these complexes the rate of hydrolysis was calculated for the second hydrolysis reaction. It is proposed that all five complexes react with the same S_N1CB mechanism. This mechanism applies to the base hydrolysis of many octahedral metal centres and evidence such as positive activation entropy values and absorption spectral changes also indicate the applicability of this mechanism for platinum(IV) complexes.

REFERENCES

1. J. Reedijk, A.M.J. Fichtinger-Schepman, A.T. van Oosterom and P. van de Putte, Platinum amine coordination compounds as anti-tumour drugs. Molecular aspects of the mechanism of action., *Struct. Bond. (Berlin)*, **67** (1987) 53.

2. B. Rosenberg, Cisplatin: Its history and possible mechanisms of action., In A.W. Prestayko, S.T. Crooke and S.K. Carter, editors, Cisplatin: Current status and new developments., Chapter 2, pages 9-20, Academic Press, New York, 1980.

3. S.E. Sherman and S.J. Lippard, Structural aspects of platinum anticancer drug interactions with DNA., *Chem. Rev.*, **87** (1987) 1153.

4. J. Reedijk, The mechanism of action of platinum anti-tumour drugs., *Pure Appl. Chem.*, **59** (1987) 181.

5. B. Rosenberg, L. van Camp and T. Krigas, Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode., *Nature*, **205** (1965) 698.

6. B. Rosenberg, L. van Camp, E.B. Grimley and A.J. Thomson, The inhibition of growth or cell division in *Escherichia coli* by different ionic species of platinum(IV) complexes., *J. Biol. Chem.*, **242** (1967) 1347.

7. B. Rosenberg, E. Renshaw, L. van Camp, J. Hartwick and J. Drobnik, Platinum-induced filamentous growth in *Esherichia coli.*, *J. Bacteriol.*, **93** (1967) 716.

8. M.J. Cleare, Transition metal complexes in cancer chemotherapy., *Coord. Chem. Rev.*, **12** (1974) 349.

9. A.J. Thomson, R.J.P. Williams and S. Reslova, The chemistry of complexes related to *cis*-$[Pt(NH_3)_2Cl_2]$. An anti-tumour drug., *Struct. Bond. (Berlin)*, **11** (1972) 1.

10. B. Rosenberg, Some biological effects of platinum compounds. New agents for the control of tumours., *Platinum Met. Rev.*, **15** (1971) 42.

11. B. Rosenberg, L. van Camp, J.E. Trosko and V.H. Mansour, Platinum compounds: a new class of potent antitumour agents., *Nature*, **222** (1969) 385.

12. B. Rosenberg and L. van Camp, The successful regression of large solid sarcoma 180 tumours by platinum compounds., *Cancer Res.*, **30** (1970) 1799.

13. a) M. Peyrone, De l'action de l'ammoniaque sur le protochlorure de platine., *Annalen der Chemie und Pharmacie*, **51** (1844) 1.
b) M. Peyrone, De l'action de l'ammoniaque sur le protochlorure de platine., *Annalen der Chemie und Pharmacie*, **55** (1845) 205.

14. A. Werner, New Ideas on Inorganic Chemistry, Longmans, Green and Co., London, translated by E.P. Hedley from the second German edition, 1911.

15. G.H.W. Milburn and M.R. Truter, The crystal structures of *cis*- and *trans*-dichlorodiammineplatinum(II)., *J. Chem. Soc. (A)*, (1966) 1609.

16. D.J. Digby, H.J. Wallace (Jr), D. Albert and J.F. Holland, Diamminodichloroplatinum in the chemotherapy of testicular tumours., *The J. Urol.*, **112** (1974) 100.

17. C.F.J. Barnard, Platinum anti-cancer agents - twenty years of continuing development., *Platinum Met. Rev.*, **33** (1989) 162.

18. E. Cvitkovic, J. Spaulding, V. Bethune, J. Martin and W.F. Whitmore, Improvement of *cis*-dichlorodiammineplatinum(II) (NSC 119875). Therapeutic index in an animal model., *Cancer (Philadelphia)*, **39** (1977) 1357.

19. B. Rosenberg, Fundamental studies with cisplatin., *Cancer (Philadelphia)*, **55** (1985) 2303.

20. R.J. Woodman, A.E. Sirica, M. Gang, I. Kline and J.M. Venditti, The enhanced therapeutic effect of *cis*-platinum(II) diamminedichloride against L1210 leukemia when combined with cyclophosphamide or 1,2-bis(3,5-dioxopiperazine-1-yl)propane or several other antitumour agents., *Chemother.*, **18** (1973) 169.

21. R.B. Weiss and M.C. Christian, New cisplatin analogues in development., *Drugs*, **46** (1993) 360.

22. L.H. Einhorn and J. Donohue, *Cis*-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer., *Ann. Intern. Med.*, **87** (1977) 296.

23. M.J. Cleare and J.D. Hoeschele, Studies on the antitumour activity of group VIII transition metal complexes. Part I. Platinum(II) complexes., *Bioinorg. Chem.*, **2** (1973) 187.

24. T.A. Connors, M. Jones, W.C.J. Ross, P.D. Braddock, A.R. Khokhar and M.L. Tobe, New platinum complexes with anti-tumour activity., *Chem.-Biol. Interact.*, **5** (1972) 415.

25. M.J. Cleare, P.C. Hydes, B.W. Malerbi and D.M. Watkins, Antitumour platinum complexes: Relationship between chemical properties and activity., *Biochemie*, **60** (1978) 835.

26. M.J. Cleare, P.C. Hydes, D.R. Hepburn and B.W. Malerbi, Antitumour platinum complexes: Structure and activity relationships., In A.W. Prestayko, S.T. Crooke and S.K. Carter, editors, Cisplatin: Current status and new developments., Chapter 9, pages 149-170, Academic Press, New York, 1980.

27. M.A. Tucker, C.B. Colvin and D.S. Martin (Jr), Substitution reactions of trichloroammineplatinate(II) ion and the *trans* effect., *Inorg. Chem.*, **3** (1964) 1373.

28. M.L. Tobe and A.R. Khokhar, Structure, activity, reactivity and solubility relationships of platinum diamine complexes., *J. Clin. Hematol. Oncol.*, **7** (1977) 114.

29. P.D. Braddock, T.A. Connors, M. Jones, A.R. Khokhar, D.H. Melzack and M.L. Tobe, Structure and activity relationships of platinum complexes with anti-tumour activity., *Chem.-Biol. Interact.*, **11** (1975) 145.

30. C.F.J. Barnard, M.J. Cleare and P.C. Hydes, Second generation platinum anticancer compounds., *Chem. in Brit.*, (1986) 1001.

31. E.W. Stern, The search for new platinum antitumour agents. Progress, problems and prospects., In M. Nicolini, editor, Platinum and other metal coordination compounds in cancer chemotherapy., Pages 519-526, Martinus Nijhoff Publishing, 1988.

32. J.H. Burchenal, K. Kalaher, K. Dew, L. Lokys and G. Gale, Studies of cross-resistance, synergistic combinations and blocking of activity of platinum derivatives., *Biochemie*, **60** (1978) 961.

33. J.H. Burchenal, K. Kalaher, T. O'Toole and J. Chisholm, Lack of cross-resistance between certain platinum coordination compounds in mouse leukemia., *Cancer Res.*, **37** (1977) 3455.

34. G.R. Gibbons. S. Wyrick and S.G. Chaney, Rapid reduction of tetrachloro(D,L-*trans*)1,2-diaminocyclohexaneplatinum(IV) (tetraplatin) in RPMI 1640 tissue culture medium., *Cancer Res.*, **49** (1989) 1402.

35. P. Soulie, E. Raymond, S. Brienza and E. Cvitkovic, Oxaliplatine: Le premier DACH platine en clinique., *Bull. Cancer*, **84** (1997) 665.

36. M.J. McKeage and L.R. Kelland in *Molecular Aspects of Anti-cancer Drug - DNA Interactions*, S. Neidle and M.J. Waring (eds.), CRC Press Inc., Boca Raton, USA, **1** (1993) 169.

37. C.F.J. Barnard, J.F. Vollano, P.A. Chaloner and S.Z. Dewa, Studies on the oral anticancer drug JM-216: Synthesis and characterisation of isomers and related complexes., *Inorg. Chem.*, **35** (1996) 3280.

38. A. Eastman, Glutathione mediated activation of anticancer platinum(IV) complexes., *Biohem. Pharm.*, **36** (1987) 4177.

39. K.J. Mellish and L.R. Kelland, Mechanisms of acquired resistance to the orally active platinum-based anti-cancer drug JM-216 to two human ovarian carcinoma cell lines., *Cancer Res.*, **54** (1994) 6194.

40. K.J. Mellish, L.R. Kelland and K.R. Harrap, In vitro platinum drug chemosensitivity of human cervical squamous cell carcinoma cell lines with intrinsic and acquired resisitance to cisplatin., *Br. J. Cancer*, **68** (1993) 240.

41. P.J. Ferguson, Mechanisms of resistance of human tumours to anticancer drugs of the platinum family: A review., *The J. Otolaryngology*, **24** (1995) 242.

42. D.B. Zamble and S.J. Lippard, Cisplatin and DNA repair in cancer chemotherapy., *Trends in Biological Sciences*, **20** (1995) 435.

43. B. Lippert, Platinum nucleobase chemistry, in S.J. Lippard, editor, Progress in Inorganic Chemistry, Vol. 37, Chapter 1, pages 1-97, John Wiley and Sons, New York, 1989.

44. S.E. Miller and D.A. House, The hydrolysis products of *cis*-diamminedichloroplatinum(II) 1. The kinetics of formation and anation of the *cis*-diammine(aqua)chloroplatinum(II) cation in acidic aqueous solution., *Inorg. Chim. Acta*, **161** (1989) 131.

45. S.E. Miller and D.A. House, The hydrolysis products of *cis*-diamminedichloroplatinum(II) 2. The kinetics of formation and anation of the *cis*-diamminedi(aqua)platinum(II) cation., *Inorg. Chim. Acta*, **166** (1989) 189.

46. S.E. Miller and D.A. House, The hydrolysis products of *cis*-diamminedichloroplatinum(II) 3. Hydrolysis kinetics at physiological pH., *Inorg. Chim. Acta*, **173** (1990) 53.

47. S.E. Miller, Huo Wen, D.A. House, W.T. Robinson, The hydrolysis products of *cis*-diamminedichloroplatinum(II) 4. Metal-ion-assisted aquation of *cis*-$PtCl_2(NH_3)_2$ and the structure of *cis*-$[PtCl_2(NH_3)_2 \cdot (HgCl_2)_3]_n$., *Inorg. Chim. Acta*, **184** (1991) 111.

48. S.E. Miller and D.A. House, The hydrolysis products of *cis*-diamminedichloroplatinum(II) 5. The anation kinetics of *cis*-$Pt(X)(NH_3)_2(OH_2)^+$ (X=Cl, OH) with glycine, monohydrogen malonate and chloride., *Inorg. Chim. Acta*, **187** (1991) 125.

49. S.E. Miller, K.J. Gerard and D.A. House, The hydrolysis products of *cis*-diamminedichloroplatinum(II) 6. A kinetic comparison of the *cis*- and *trans*-isomers and other *cis*-di(amine)di(chloro)platinum(II) compounds., *Inorg. Chim. Acta*, **190** (1991) 135.

50. E. Koubek and D.A. House, The hydrolysis products of *cis*-diamminedichloroplatinum(II) 7. The rate of the hydrogen isotope exchange reaction., *Inorg. Chim. Acta*, **191** (1992) 103.

51. C.J. Abraham, K.J. Gerard and D.A. House, The hydrolysis products of *cis*-diamminedichloroplatinum(II) 8. Kinetics of the base hydrolysis of $PtCl_2(AA)$ (AA=en, chxn, tn, Me_2tn) and *trans*-$PtCl_2(NH_3)_2$., *Inorg. Chim. Acta*, **209** (1993) 119.

52. D.P. Bancroft, C.A. Lepre and S.J. Lippard, ^{195}Pt NMR kinetic and mechanistic studies of *cis*- and *trans*-diamminedichloroplatinum(II) binding to DNA., *J. Am. Chem. Soc.*, **112** (1990) 6860.

53. F. Aprile and D.S. Martin, Chlorotriammineplatinum(II) ion. Acid hydrolysis and isotopic exchange of the chloride ligands., *Inorg. Chem.*, **1** (1962) 551.

54. J.W. Reishus and D.S. Martin (Jr), *Cis*-dichlorodiammineplatinum(II). Acid hydrolysis and isotopic exchange of the chloride ligands., *J. Am. Chem. Soc.*, **83** (1961) 2457.

55. H.D.K. Drew, F.W. Pinkard, W. Wradlow and E.G. Cox, The structure of the isomeric diamminoplatinous chlorides. Discovery of a third isomeride., *J. Chem. Soc.*, **135** (1932) 988.

56. B. Rosenberg, Platinum complexes - DNA interactions and anticancer activity., *Biochem.*, **60** (1978) 859.

57. J.R. Peramareddi and A.W. Adamson, Photochemistry of complex ions. V. The photochemistry of some square planar platinum(II) complexes., *J. Phys. Chem.*, **72** (1978) 414.

58. A.I. Stetsenko and L.B. Sel'derkhanova, Kinetics of acid hydrolysis of certain platinum(II) *cis* non-electrolytes., *Russ. J. Inorg. Chem.*, **26** (1981) 164.

59. J.E. Teggins, K.W. Lee, J.M. Baker and E.D. Smith, Kinetics of the *cis*-dichlorodiammineplatinum(II) - oxalate reaction in aqueous solution., *J. Coord. Chem.*, **1** (1971) 215.

60. J.L. Butour, A.M. Mazard and J-P. Macquet, Kinetics of the reaction of *cis*-platinum compounds with DNA *in vitro.*, *Biochem. Biophys. Res. Comm.*, **133** (1985) 347.

61. R.N. Bose, R.D. Cornelius and R.E. Viola, Phosphorus-31-NMR and kinetic studies of the formation of ortho-, pyro- and triphosphato complexes of *cis*-dichlorodiammineplatinum(II)., *J. Am. Chem. Soc.*, **106** (1984) 3336.

62. R.N. Bose, R.D. Cornelius and R.E. Viola, Multinuclear NMR studies and the kinetics of formation of platinum(II) - adenine nucleotide complexes., *J. Am. Chem. Soc.*, **108** (1986) 4403.

63. C.M. Riley, L.A. Sternson, A.J. Repta and S.A. Slyter, Reactivity of *cis*-dichlorodiammineplatinum(II) (cisplatin) toward selected nucleophiles., *Polyhedron*, **1** (1982) 201.

64. C.M. Riley, L.A. Sternson, A.J. Repta and R.W. Siegler, High-performance liquid chromatography of platinum complexes on solvent generated anion exchangers. III. Application to the analysis of cisplatin in urine using automated column switching., *J. Chromatog.*, **229** (1982) 373.

65. A.A. Hincal, D.F. Long and A.J. Repta, Cis-platin stability in aqueous parenteral vehicles., *J. Parent. Drug Assoc.*, **33** (1979) 107.

66. R.F. Greene, D.C. Chatterji, P.K. Hiranaka and J.F. Gallelli, Stability of cisplatin in aqueous solution., *Am. J. Hosp. Pharm.*, **36** (1079) 38.

67. D. Banerjea, F. Basolo and R.G. Pearson, Mechanism of substitution reactions of complex ions. XII. Reactions of some platinum(II) complexes with various reactants., *J. Am. Chem. Soc.*, **79** (1957) 4055.

68. V.D. Panasyuk and N.F. Malashok, Kinetic studies of the acid hydrolysis of various platinum(II) complexes in aqueous solution., *Russ. J. Inorg. Chem.*, **13** (1968) 1405.

69. E. Segal and J-B. Le Pecq, Role of ligand exchange processes in the reaction kinetics of the antitumour drug *cis*-diamminedichloroplatinum(II) with its targets., *Cancer Res.*, **45** (1985) 492.

70. K.W. Lee and D.S. Martin, *Cis*-dichlorodiammineplatinum(II). Aquation equilibria and isotopic exchange of chloride ligands with free chloride and tetrachloroplatinate., *Inorg. Chim. Acta*, **17** (1976) 105.

71. A.A. Grinberg and A.A. Korableva, Hydrolysis of isomeric diammine complexes $[PtCl_2(NH_3)_2]$., *Russ. J. Inorg. Chem.*, **13** (1968) 565.

72. K.M. Comess and S.J. Lippard in *Molecular Aspects of Anti-cancer Drug - DNA Interactions*, S. Neidle and M.J. Waring (eds.), CRC Press Inc., Boca Raton, USA, **1** (1993) 134.

73. M.J. Bloemink and J. Reedijk, Cisplatin and derived anticancer drugs: Mechanism and current status of DNA binding., *Metal-ions in Biological Systems*, **32** (1996) 641.

74. S.E. Sherman and S.J. Lippard, Structural aspects of platinum anticancer drug interactions with DNA., *Chem. Rev.*, **87** (1987) 1153.

75. P.M. Takahara, A.C. Rosenzweig, C.A. Frederick and S.J. Lippard, Crystal structure of double stranded DNA containing the major adduct of the anticancer drug cisplatin., *Nature*, **377** (1995) 649.

76. S.E. Sherman, D. Gibson, A.H-J. Wang and S.J. Lippard, Crystal and molecular structure of *cis*-[$Pt(NH_3)_2d(pGpG)$], the principal adduct formed by *cis*-diamminedichloroplatinum(II) with DNA., *J. Am. Chem. Soc.*, **110** (1988) 7368.

77. S.E. Sherman, D. Gibson, A.H-J. Wang and S.J. Lippard, Xray structure of the major adduct of the anticancer drug cisplatin with DNA: *cis*-[$Pt(NH_3)_2d(pGpG)$]., *Science*, **203** (1985) 412.

78. G.L. Cohen, W.R. Bauer, J.K. Barton and S.J. Lippard, Binding of *cis*- and *trans*-dichlorodiammineplatinum(II) to DNA: Evidence for unwinding and shortening of the double helix., *Science*, **203** (1978) 1014.

79. N.P. Johnson, A.M. Mazard, J. Escalier and J.P. Macquet, Mechanism of the reaction between *cis*-[$PtCl_2(NH_3)_2$] and DNA *in vitro*., *J. Am. Chem. Soc.*, **107** (1985) 6376.

80. P.M. Takahara, C.A. Frederick and S.J. Lippard, Crystal structure of the anticancer drug cisplatin bound to duplex DNA., *J. Am. Chem. Soc.*, **118** (1996) 12309.

81. P.M. Pil and S.J. Lippard, Specific binding of chromosomal protein HMG1 to DNA damaged by the antiancer drug cisplatin., *Science*, **256** (1992) 234.

82. A. Eastman, Reevaluation of interaction of *cis*-dichloro(ethylenediamine) platinum(II) with DNA., *Biochem.*, **25** (1986) 3912.

83. C. Perez, M. Leng and J-M. Malinge, Rearrangement of interstrand cross-links into intrastrand cross-links in *cis*-diamminedichloroplatinum(II)-modified DNA., *Nucl. Acids Res.*, **25** (1997) 896.

84. C.H. Langford and H.B. Gray, Ligand substitution processes., W.A. Benjamin, New York, 1965.

85. E.E. Blatter, J.F. Vollano, B.S. Krishman and J.C. Dabrowiak, Interaction of the antitumour agents *cis, cis, trans*-$Pt^{IV}(NH_3)_2Cl_2(OH)_2$ and *cis, cis, trans*-$Pt^{IV}[(CH_3)_2CHNH_2]_2Cl_2(OH)_2$ and their reduction products with PM2 DNA., *Biochem.*, **23** (1984) 4817.

86. J.L van der Veer, A.R. Peters and J. Reedijk, Reaction products from platinum(IV) amine compounds and 5'-GMP are mainly bis(5'-GMP)platinum(II) amine adducts., *J. Inorg. Biochem.*, **26** (1986) 137.

87. L. Pendyala, J.W. Cowens, G.B. Chheda, S.P. Dutta and P.J. Creaven, Identification of *cis*-dichloro-bis-isopropylamine platinum(II) as a major metabolite of iproplatin in humans., *Cancer Res.*, **48** (1988) 3533.

88. A. Peloso, Effects of geometric configuration and steric hindrance on rates and mechanisms of oxidation of diaminedichloroplatinum(II) complexes by tetrachloroaurate(III) ions., *J. Chem. Soc. Dalton*, (1983) 1285.

89. T. Shi, J. Berglund and L.I. Elding, Kinetics and mechanism for the reduction of *trans*-dichlorotetracyanoplatinate(IV) by thioglycolic acid, L-cysteine, DL-penicillamine and glutathione in aqueous solution., *Inorg. Chem.*, **35** (1996) 3498.

90. T.Shi, J. Berglund and L.I. Elding, Reduction of *trans*-dichloro- and *trans*-dibromo-tetracyanoplatinate(IV) by L-methionine., *J. Chem. Soc. Dalton*, (1997) 2073.

91. R.N. Bose and E.L. Weaver, A long-lived ascorbate radical in the platinum(II) catalysed reductions of platinum(IV) antitumor drugs., *J. Chem. Soc. Dalton*, (1997) 1797.

92. D.A. House, unpublished research.

93. D.J. Evans and M. Green, The rate of reduction of *cis*-, *cis*-, *trans*-$[Pt^{IV}(NH_2Pr^i)_2Cl_2(OH)_2]$, CHIP, the anti-cancer drug by ascorbic acid., *Inorg. Chim. Acta*, **130** (1987) 183.

94. U.S. Mehrotra, M.C. Agrawal and S.P. Mushran, Reduction of hexachloroplatinate by ascorbic acid., *J. Inorg. Nucl. Chem.*, **32** (1970) 2325.

95. K.K. Sen Gupta and P.K. Sen, Kinetics of the oxidation of hydroxylamine by platinum(IV)., *J. Inorg. Nucl. Chem.*, **39** (1977) 1651.

96. K.K. Sen Gupta, S. Das and S. Sen Gupta, Kinetics of oxidation of sulphite by hexachloroplatinate(IV) in acidic solution., *Transition Met. Chem.*, **12** (1987) 414.

97. E.G. Talman, W. Brunning, J. Reedijk, A.L. Spek and N. Veldman, Crystal and molecular structures of asymmetric *cis*- and *trans*-platinum(II/IV) compounds and their reactions with DNA fragments., *Inorg. Chem.*, **36** (1997) 854.

98. P. Chandyot and Y-T. Fanchiang, Base-promoted reduction of *trans*-dibromotetracyanoplatinate(IV) and hypobromous acid oxidation of tetracyanoplatinate(II). Kinetics and mechanisms., *Inorg. Chem.*, **24** (1985) 3535.

99. P. Chandyot and Y-T. Fanchiang, Kinetics and mechanisms of the reduction of *trans*-dibromotetracyanoplatinate(IV) complexes by inorganic anions., *Inorg. Chem.*, **24** (1985) 3532.

100. A. Peloso, Role of steric hindrance of methyl groups on the rates of reduction of N-methyl substituted ethylenediamine complexes of platinum(IV)., *Polyhedron*, **11** (1992) 2187.

101. A. Peloso, An investigation on the influence of coordinated aliphatic amines on the rates of reduction of tetrachlorodiamineplatinum(IV) complexes., *J. Chem. Soc. Dalton*, (1984) 249.

102. A. Peloso, Role of the ligands in affecting the stoichiometry and the rate of reactions between platinum(IV) and platinum(II) complexes., *Polyhedron*, **10** (1991) 2191.

103. K.G. Moodley and M.J. Nicol, Kinetics of the reduction of platinum(IV) by tin(II) and copper(I) in aqueous chloride solutions., *J. Chem. Soc. Dalton*, (1977) 239.

104. C.S. Glennon, T.D. Hand and A.G. Sykes, Kinetic data for outer-sphere V^{2+} and $[Ru(NH_3)_6]^{2+}$ reductions of platinum(IV) complexes and a correlation of rate constants., *J. Chem. Soc. Dalton*, (1980) 19.

105. T.J. Harrigan and R.C. Johnson, Oxidation of the tetraammineplatinum(II) cation with the peroxydisulfate ion and with hydrogen peroxide. Synthesis of sulfatoplatinum(IV) complexes., *Inorg. Chem.*, **16** (1977) 1741.

106. S.O. Dunham, R.D. Larsen and E.H. Abbott, NMR investigation of the H_2O_2 oxidation of platinum(II) complexes. Crystal and molecular structures of sodium *trans*-dihydroxybis(malonato)platinate(IV).$6H_2O$ and sodium *trans*-dihydroxybis(oxalato)-platinate(IV).$6H_2O$., *Inorg. Chem.*, **32** (1993) 2049.

107. S.O. Dunham, R.D. Larsen and E.H. Abbott, NMR investigation of the formation of oxalato, malonato and 2-methylmalonato complexes of platinum(II). Crystal and molecular structures of K-antibis(2-methylmalonato)platinate(II).$2H_2O$ and $K_2[PtCl_2(oxalato)].H_2O$., *Inorg. Chem.*, **30** (1991) 4328.

108. L. Drougge and L.I. Elding, Kinetics and mechanism for oxidation of tetracyanoplatinate(II) by chlorine and hypochlorous acid and for hydrolysis of chlorine in aqueous solution., *Inorg. Chem.*, **24** (1985) 2292.

109. J. Halpern and M. Pribanic, The oxidation of platinum(II) complexes by hexachloroiridate(IV). Evidence for the intermediate formation of platinum(III)., *J. Am. Chem. Soc.*, **90** (1968) 5942.

110. A. Peloso, A kinetic investigation on the oxidation of platinum(II) complexes by hexachloroiridate(IV). Role of steric hindrance., *J. Chem. Soc. Dalton*, (1988) 577.

111. A. Peloso, Kinetic studies on the oxidation of ethylenebis(pyridyl) and bis(ethylenediamine) platinum(II) complexes by hexachloroiridate(IV)., *J. Chem. Soc. Dalton,* (1987) 1473.

112. A. Peloso, Oxidation of platinum(II) complexes by tetrachloroaurate(III) ions in the presence of tetraethylammonium chloride., *Coord. Chem. Rev.*, **16** (1975) 95.

113. A. Peloso, Effects of the four in-plane ligands on the rates of inner-sphere oxidation reactions of tetraammine- and diamminediamineplatinum(II) complexes., *Gazz. Chim. Ital.*, **115** (1985) 625.

114. W.R. Mason, Platinum(II)-catalysed substitutions of platinum(IV) complexes., *Coord. Chem. Rev.*, **7** (1972) 241.

115. W. Mason, The mechanism of bromine oxidation of tetracyanoplatinate(II) and tetraammineplatinum(II) ions., *Inorg. Chem.*, **10** (1971) 1914.

116. S.V. Zemskov, B.V. Ptitsyn, V.N. Lyubimov and V.F. Malakov, Oxidation of platinum(II) complexes., *Russ. J. Inorg. Chem.*, **12** (1967) 648.

117. B. Lippert, *Trans*-diammineplatinum(II): What makes it different from *cis*-DDP? Coordination chemistry of a neglected relative of cisplatin and its interaction with nucleic acids., *Met. Ions in Biolog. Systems.*, **33** (1996) 105.

118. N. Farrell, Current status of structure-activity relationships of platinum anticancer drugs: Activation of the *trans* geometry., *Met. Ions in Biolog. Systems.*, **32** (1996) 603.

119. L.R. Kelland, C.F.J. Barnard, K.J. Mellish, M. Jones, P.M. Goddard, M. Valenti, A. Bryant, B.A. Murrer and K.R. Harrap, A novel *trans*-platinum coordination complex possessing *in vitro* and *in vivo* antitumour activity., *Cancer Res.*, **54** (1994) 5618.

120. Applied Photo-Physics Bio-Sequential SX-18MV Stopped-Flow Reaction Analyser, Software manual, Applied Photo-Physics Ltd., Leatherhead, UK, 1995.

121. *Calculations in Advanced Physical Chemistry*, 3rd edition, P.J.F. Griffiths and J.D.R. Thomas, Edward Arnold, 1983.

122. *Physical Chemistry*, 4th edition, P.W. Atkins, Oxford University Press, 1990.

123. *Inorganic Chemistry*, D.E. Schriver, P.W. Atkins and C.H. Langford, Oxford University Press, 1990.

124. J-L. Jestin, J-C. Chottard, U. Frey, G. Laurenczy and A.E. Merbach, Mechanism of aquation of bicycloalkyl-substituted (ethylenediamine)dichloroplatinum(II) complexes: A search for the understanding of their differences in antitumor activity., *Inorg. Chem.*, **33** (1994) 4277.

125. P.J. Bednarski and B. Trümbach, Use of reversed phase HPLC for determination of the hydrolysis rate constants of dichloro(1,2-diarylethylendiamine)platinum(II) complexes., *Transition Met. Chem.*, **19** (1994) 513.

126. Y.T. Fanchiang, Reaction intermediates of *cis*-diammineaqua(hydroxo)-platinum(II) with guanosine-5'-monophosphate characterised by proton magnetic resonance spectroscopy., *J. Chem. Soc. Dalton*, (1988) 135.

127. A. Woollins and B. Rosenberg, High performance liquid chromatography studies on the interaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with guanine and methylated guanines., *J. Inorg. Biochem.*, **20** (1984) 23.

128. S. Eapen, M. Green and I.M. Ismail, Kinetic studies on the diaqua form of cisplatin and various nucleobases., *J. Inorg. Biochem.*, **24** (1985) 233.

129. V. Saudek, H. Pivcova, D. Naskova and J. Drobnik, Reaction of Pt(II) antitumour drugs with selected nucleophiles III. *Cis*-$[Pt(NH_3)_2Cl_2]$ and diamminomalonato-Pt(II) complexes compared in the reaction with glycine and l-histidine., *J. Inorg. Biochem.*, **24** (1985) 13.

130. S.K. Miller and L.G. Marzilli, Interactions of platinum antitumour agents with guanine nucleosides and nucleotides, ^{195}Pt and ^{1}H NMR spectroscopic characterisation of compound (III)., *Inorg. Chem.*, **24** (1985) 2421.

131. V. Saudek, H. Pivcova, D. Naskova and J. Drobnik, The reaction of Pt(II) antitumour drugs with selected nucleophiles II. Preparation and characterisation of coordination compounds of Pt(II) and l-histidine., *J. Inorg. Biochem.*, **23** (1985) 55.

132. A.T. M. Marcelis, C. Erkelens and J. Reedijk, The interaction of aquated platinum(II) compounds with purine mononucleotides., *Inorg. Chim. Acta*, **91** (1984) 129.

133. F.J. Dijt, G.W. Canters, J.H.J. den Hartog, A.T.M. Marcelis and J. Reedijk, Reaction products of *cis*-diammineplatinum(II) compounds with 5'-guanosine monophosphate characterized by high-frequency proton NMR., *J. Am. Chem. Soc.*, **106** (1984) 3644.

134. D.J. Evans, N.R. Ford and M. Green, Kinetic and thermodynamic selectivity in the reactions of the diaqua form of cisplatin with 3'- and 5'-guanosine monophosphoric acid., *Inorg. Chim. Acta*, **125** (1986) L39.

135. D.J. Evans, M. Green and R. van Eldik, The kinetics and mechanism of the reaction of 2'-deoxy-5'-guanosinemonophosphoric acid and the diaqua form of cisplatin., *Inorg. Chim. Acta*, **128** (1987) 27.

136. B. Odenheimer and W. Wolf, Reactions of cisplatin with sulfur containing amino acids and peptides I. Cysteine and glutathione., *Inorg. Chim. Acta*, **66** (1982) L41.

137. S. Murakami, K. Saito, A. Muromatsu, M. Moriyasu, A. Kato and Y. Hashimoto, Studies on the reactions of $PtCl_2$en, *cis*-$Pt(NH_3)_2Cl_2$ and their aqua species with adenosine, deoxyadenosine and adenine using ion-pair HPLC., *Inorg. Chim. Acta*, **152** (1988) 91.

138. G.M. Clore and A.M. Gronenborn, Kinetic and structural studies on the intermediates formed in the reactions of 5'-adenosine monophosphate and 5'-guanosinemonophosphate with *cis*-dichlorodiammineplatinum(II) using ^{1}H and ^{195}Pt magnetic resonance spectroscopy., *J. Am. Chem. Soc.*, **104** (1982) 1369.

139. W.M. Scovell and T. O'Connor, Interaction of aquated *cis*-[$Pt(NH_3)_2Cl_2$] with nucleic acid constituents I. Ribonucleosides., *J. Am. Chem. Soc.*, **99** (1977) 120.

140. G.Y.H. Chu and R.S. Tobias, Heavy metal-nucleotide interactions. 8. Binding of *cis*-diammineplatinum(II) and ethylenediamineplatinum(II) to inosine, 1-methylinosine and 5'-inosine monophosphate in aqueous solution., *J. Am. Chem. Soc.*, **98** (1976) 2641.

141. T.G. Appleton, J.W. Connor, J.R. Hall and P.D. Prenzler, NMR study of the reactions of the cis-diamminediaquaplatinum(II) cation with glutathione and amino acids containing a thiol group., *Inorg. Chem.*, **28** (1989) 2030.

142. N. Goswami, L.L. Bennett-Slavin and R.N. Bose, New insights into the mechanism of the cisplatin-guanosine 5'-monophosphate reaction., *J. Chem. Soc. Chem. Commun.*, (1989) 432.

143. A.I. Stetsenko, K.I. Yakovlev and S.A. D'yachenko, Platinum(II) complexes of purine and pyrimidine bases and their nucleosides., *Russ. Chem. Rev.*, **56** (1987) 875.

144a. A. Vogel, *Textbook of Quantitative Analysis*, Longmans, Green and Co., London, p274, 3rd Edn. (1961).

144b. A. Vogel, *Textbook of Quantitative Analysis*, Longmans, Green and Co., London, p368, 3rd Edn. (1961).

145. L. Canovse, L. Cattalini, G. Chessa and M.L. Tobe, Kinetics of the displacement of cyclobutane-1,1-dicarboxylate from diammine(cyclobutane-1,1-dicarboxylato)platinum(II) in aqueous solution., *J. Chem. Soc. Dalton*, (1988) 2135.

146. A. Woollins and B. Rosenberg, High performance liquid chromatography studies on the interactions of *cis*-$Pt(NH_3)_2(OH_2)_2^{2+}$ with guanine and methylated guanines., *J. Inorg. Biochem.*, **20** (1984) 23.

147. G.Y.H. Chu, R.E. Duncan and R.S. Tobias, Heavy metal-nucleoside interactions. 10. Binding of cis-diammineplatinum(II) to cytidine and uridine in aqueous solution: Necessary conditions for formation of platinum-uridine blues., *Inorg. Chem.*, **16** (1977) 2625.

148. W.M. Scovell and T. O'Connor, Interaction of aquated *cis*-[$Pt(NH_3)_2$] with nucleic acid constituents. 1. Ribonucleosides., *J. Am. Chem. Soc.*, **99** (1977) 120.

149. A.T.M. Marcelis, C.G. van Kralingen and J. Reedijk, The interactions of *cis* and *trans* diammineplatinum(II) compounds with 5'-guanosine monophosphate and 5'-deoxyguanosine monophosphate. A proton NMR investigation., *J. Inorg. Biochem.*, **13** (1980) 213.

150. A.T.M. Marcelis, C. Erkelens and J. Reedijk, The interaction of aquated platinum(II) compounds with purine mononucleotides., *Inorg. Chim. Acta*, **91** (1984) 129.

151. B. Van Hemelryck, J-P. Girault, G. Chottard, P. Valadon, A. Laoui and J-C. Chottard, Sequence-dependent platinum chelation by adenylyl (3'-5')guanosine and guanylyl (3'-5')adenosine reacting with *cis*-diamminedichloroplatinum(II) and its diaqua derivative., *Inorg. Chem.*, **26** (1987) 787.

152. A. Laoui, J. Kozelka and J-C. Chottard, *Cis*-diamminediaquaplatinum(II) selectivity for GpG: Influence of the adjacent base on the first platination step., *Inorg. Chem.*, **27** (1988) 2751.

153. J. Arpalahti and B. Lippert, Coordination of aquated cis-platinum(II) diamines to purine nucleosides. Kinetics of complex formation., *Inorg. Chem.*, **29** (1990) 104.

154. J. Arpalahti, Kinetics for pH-dependent complexation of aquated cis-diammineplatinum(II) with inosine and 1-methylinosine., *Inorg. Chem.*, **29** (1990) 4598.

155. W.P. Johnson, J.D. Hoeschele and R.O. Rahn, Kinetic analysis of the *in vitro* binding of radioactive *cis*- and *trans*-dichlorodiammineplatinum(II) to DNA., *Chem.-Biol. Interactions*, **30** (1980) 151.

156. C.I. Sanders and D.S. Martin, Acid hydrolysis of $[PtCl_4^{2-}]$ and $[PtCl_3(H_2O)^-]$., *J. Am. Chem. Soc.*, **83** (1961) 807.

157. T.G. Appleton, A.J. Bailey, K.J. Barnham and J.R. Hall, Aspects of solution chemistry of *trans*-platinum complexes., *Inorg. Chem.*, **31** (1992) 3077.

158. M. Mikola and J. Arpalahti, Kinetics and mechanism of the complexation of transplatin with the purine nucleoside inosine in aqueous solution., *Inorg. Chem.*, **33** (1994) 4439.

159. K.J. Gerard, J. Morgan, P.J. Steel and D.A. House, The synthesis, hydrolysis kinetics and structures of nickel(II) and cobalt(III) complexes of meso and racemic 1,2-diaminocyclohexane., *Inorg. Chim. Acta*, **260** (1997) 27.

160. T.G. Appleton, R.J. Hall, S.F. Ralph and C.S.M. Thompson, NMR study of acid-base equilibria and other reactions of ammine platinum complexes with aqua and hydroxo ligands., *Inorg. Chem.*, **28** (1989) 1989.

161. T.G. Appleton, K.J. Barnham and R.J. Hall, *Proc. Combined Royal Australian Chemical Institute, Inorganic Division and the New Zealand Institute of Chemistry, Inorganic and Organometallic Specialist Group Meeting, University of Waikato, Hamilton*, 1991, Poster P2-44.

162. R.B. Martin, in S.J. Lippard (ed.), *Metal Chemotherapeutic Agents*, ACS Symposium Series 209, 1983, p. 231.

163. J.L. van der Veer, A.R. Peters and J. Reedijk, Reaction products from platinum(IV) amine compounds and 5'-GMP are mainly bis-(5'-GMP) platinum(II) amine adducts., *J. Inorg. Biochem.*, **26** (1986) 137.

164. D.A. House in *Comprehensive Coordination Chemistry*, G. Wilkinson Ed., Pergamon Press, Oxford, U.K., **2** (1987) 23.

165. C.D. Hubbard and R. van Eldik, Use of high pressure techniques for measuring reaction rates in liquid solutions., *Instr. Sci. and Tech.*, **23** (1995) 1.

166. S. Suvachittanont and R. van Eldik, Steric and nucleophilic control over the versatile complex-formation kinetics of model *cis*-bis(amine)palladium(II) complexes with inosine and inosine 5'-monophosphate., *Inorg. Chem.*, **33** (1994) 895.

167. T. Rau and R. van Eldik, Mechanistic insight from kinetic studies on the interaction of model palladium(II) complexes with nucleic acid components., *Metal Ions in Biological Systems*, **32** (1996) 339.

168. K. Hindmarsh, D.A. House and M.M. Turnbull, The hydrolysis products of *cis*-diamminedichloroplatinum(II) 9. Chloride and bromide anation kinetics for some $[Pt^{II}(N)_2(OH_2)_2]^{2+}$ complexes and the structures of $[Pt^{IV}Br_4(N)_2]$ $((N)_2$ = en, tn)., *Inorg. Chim. Acta*, **257** (1997) 11.

169. Y. Kitamura and K. Ida, Pressure effect on the aquation velocity of cis-$Pt(NH_3)_2Cl_2$ and $Pt(en)_2Cl_2$., *Inorg. Chim. Acta*, **88** (1984) 161.

170. C.F.J. Barnard, D.M.L. Goodgame, S.D. Plank, A.M.Z. Slawin and D.J. Williams, Pt(IV) complexes as orally active antitumor agents., *Int. Conf. Coord. Chem.*, **29** (1992) P474.

171. A. Peloso, G. Dolcetti and R. Ettorre, Reduction reactions of *trans*-PtL_2X_4 complexes. Influence of the uncharged ligands L on the reduction reaction rates., *Inorg. Chim. Acta*, **1** (1967) 403.

172. A. Peloso, Kinetic studies of reversible redox reactions between platinum(IV) and platinum(II) complexes., *Gazz. Chim. Ital.*, **117** (1987) 51.

173. A.S. Meyer (Jr) and G.H. Ayres, The interaction of platinum(II) and tin(II) chlorides., *J. Am. Chem. Soc.*, **77** (1955) 2671.

174. N.N. Greenwood and A. Earnshaw, *Chemistry of the Elements*, Pergamon, Oxford, U.K., (1984) p442.

175. A. Peloso and M. Basato, The kinetics of the reduction of platinum(IV) complexes by ferrocene in hydroxylic solvents., *Coord. Chem. Rev.*, **8** (1972) 111.

176. C.K. Jørgensen, *Inorganic Complexes*, Academic Press, London (1963) pp41, 42.

177. Stability constants database, IUPAC, Academic Software, Oxford.

178. B. Bänsch, P. Martinez, J. Zuluaga, D. Uribe and R. van Eldik, Kinetics and mechanism of the oxidation of L-ascorbic acid by hexacyanoiron(III) in acidic aqueous solution. Application of high-pressure techniques., *Zeitschrift für Physikalische Chemie*, **170** (1991) 59.

179. N. Farrell in *Catalysis by Metal Complexes*, R. Ugo and B.R. James (eds.), Kluwer, Dordrecht, **11** (1989) 76.

180. M.A. Allsopp, G.J. Sewell, C.G. Rowland, C.M. Riley and R.L. Schowen, The degradation of carboplatin in aqueous solutions containing chloride or other selected nucleophiles., *Int. J. Pharm.*, **69** (1991) 197.

181. U. Frey, J.D. Ranford and P.J. Sadler, Ring opening reactions of the anticancer drug carboplatin: NMR characterization of *cis*-[$Pt(NH_3)_2$-(CBDCA-O)(5'-GMP-N7)] in solution., *Inorg. Chem.*, **32** (1993) 1333.

182. D.A. House, Kinetics and mechanism of oxidations by peroxydisulfate., *Chem. Rev.*, **62** (1962) 185.

183. W.K. Wilmarth and A. Haim in *Peroxide Reaction Mechanisms*, J.O. Edwards (ed.), Interscience, N.Y. (1962) 175.

184. J.W.L. Fordham and H.L. Williams, The persulfate-iron(II) initiator system for free radical polymerisation., *J. Am. Chem. Soc.*, **73** (1951) 4855.

185. R.G. Wilkins, *Kinetics and Mechanism of Reactions of Transition Metal Complexes*, 2nd Edn. VCH Press, Weinheim (1991) 70.

186. A.R. Khokhar, Y. Deng, Y. Kido and Z.H. Siddick, Preparation, characterisation and antitumor activity of new ethylenediamine platinum(IV) complexes containing mixed carboxylate ligands., *J. Inorg. Biochem.*, **50** (1993) 79.

187. A.A. Grinberg and A.A. Korableva, Kinetics of hydration of the isomeric salts of [$Pt(NH_3)_2Cl_4$]., *Russ. J. Inorg. Chem.*, **9** (1964) 1253.

188. R.C. Johnson, F. Basolo and R.G. Pearson, Base hydrolysis of some chloroammine platinum(IV) complexes., *J. Inorg. Nucl. Chem.*, **24** (1962) 59.

189. M. L. Tobe, Base hydrolysis of transition metal complexes., *Adv. Inorg. Bioinorg. Mech.*, **2** (1983) 1.

190. F. Basolo and R.G. Pearson, Mechanisms of inorganic reactions. A study of metal complexes in solution., 2nd Edition, John Wiley and Sons, New York, 1967.

191. F.J. Garrick, Possible acid-dissociation of metal-ammonia ions and its bearing on certain reactions., *Nature*, **139** (1937) 507.

192. H. Erlenmeyer and H. Gartner, Über die beständigkeit von $[Co(NH_3)_6](NO_3)_3$ in $H_2{}^2O$-haltigem Wasser., *Helv. Chim. Acta*, **17** (1934) 1008.

193. S.C. Chan, Octahedral cobalt(III) complexes of the chloropentammine type. Part VI. Kinetic evidence for the ion-pair mechanism of base hydrolysis of cobalt(III) complexes in aqueous solution., *J. Chem. Soc. (A)*, (1966) 1124.

194. A.A. Grinberg and A.A. Korableva, Kinetics of the alkaline hydrolysis of $[PtCl_4(NH_3)_2]$ isomers., *Russ. J. Inorg. Chem.*, **11** (1966) 409.

195. A.A. Grinberg and Y.N. Kukushkin, Kinetics of hydrolysis of some tetravalent platinum complexes., *Russ. J. Inorg. Chem.*, **6** (1961) 554.

196. T.G. Appleton, J.R. Hall and S.G. Ralph, ^{15}N and ^{195}Pt NMR spectra of platinum ammine complexes: *Trans* and *cis* influence series based on ^{195}Pt - ^{15}N coupling constants and ^{15}N chemical shifts., *Inorg. Chem.*, **24** (1985) 4685.

197. J.O Edwards, F. Monacelli and G. Ortaggi, Rate parameters for ligand replacement processes in octahedral complexes of metals in oxidation state 3., *Inorg. Chim. Acta*, **11** (1974) 47.

198. F.R. Nordmeyer, The stereochemistry of base hydrolysis of $Co(NH_3)_5X^{2+}$ and $Co(en)_2LX^{n+}$ ions., *Inorg. Chem.*, **8** (1969) 2780.

APPENDIX

APPENDIX 1: Derivation for the calculation of activation volume ($\Delta V^{\#}$).

Pressure is a fundamental physical property that can influence both thermodynamic and kinetic parameters. The relationship between pressure and these parameters can be found by considering the pressure dependence of a chemical potential μ_i of a solute species i for an ideal dilute solution.

$\mu_i = \mu_i^{+} + RT\ln x_i = \mu_i^{o} + RT\ln M_i$ (where x = mole fraction, M = molarity) (A1.1)

The pressure dependence of μ_i at constant temperature and composition equals the partial molar volume V_i of species i.

$$(\partial\mu_i^{+}/\partial P)_T = V_i \qquad \text{(A1.2)}$$

but for molarity, M_i will change with pressures in the same way as the density of the solution φ thus:

$$(\partial\mu_i^{o}/\partial P)_T = (\partial\mu_i^{o}/\partial P)_T - RT(\partial\ln\varphi/\partial P)_T$$

$$= V_i - RT\kappa \qquad \text{(A1.3)}$$

where κ is the compressibility of the solution.

Now consider a general chemical reaction of the form

$$aA + bB \Leftrightarrow cC + dD \qquad \text{(A1.4)}$$

The overall chemical potential at equilibrium should be zero thus

$$c\mu_C + d\mu_D - a\mu_A - b\mu_B = 0 \qquad \text{(A1.5)}$$

which gives

$$c\mu_C^{+} + d\mu_D^{+} - a\mu_A^{+} - b\mu_B^{+} = -RT\ln K_x \qquad \text{(A1.6)}$$

where $K_x = x_C^{c}\, x_D^{d} / x_A^{a}\, x_B^{b}$ (expressed in terms of mole fraction).

Applying the pressure derivative in (A1.2) gives

$$-RT(\partial \ln K_x/\partial P)_T = cV_C + dV_D - aV_A - bV_B$$

$$= \Delta V \qquad \text{(A1.7)}$$

where V is the reaction volume or partial molar volume change for the reaction.

Or, in the case of molarity

$$-RT(\partial \ln K_M/\partial P)_T = \Delta V - RT\kappa(c + d - a - b) \qquad \text{(A1.8)}$$

These thermodynamic expressions can be converted to the equivalent kinetic expressions.

$$aA + bB \Leftrightarrow [aA\cdots\cdots bB]^{\#} \rightarrow cC + dD \qquad \text{(A1.9)}$$

$K^{\#}$ obeys the normal thermodynamic relationships above and the experimentally measured rate constant, k, is assumed to be proportional to $K^{\#}T$. Since k then has the same concentration dimensions as $K^{\#}$ the activation volume can be given by

$$\Delta V^{\#} = -RT\ln(\partial \ln k_x/\partial P)_T \qquad \text{(A1.10)}$$

So that, in terms of molarity,

$$-RT\ln(\partial \ln k_M/\partial P)_T = \Delta V^{\#} - RT\kappa(1 - a - b)$$

$$= \Delta V^{\#} - RT\kappa(1 - n) \qquad \text{(A1.11)}$$

where n is the kinetic order of the reaction. Thus for a first-order process the expressions are identical for mole fraction and molarity.

The temperature dependence on the reaction rate gives rise to the activation enthalpy ($\Delta H^{\#}$) and the activation entropy ($\Delta S^{\#}$). The mechanistic interpretation of these, together with $\Delta V^{\#}$, is most important for any kinetic investigation.

APPENDIX 2: Derivation of Equation (3.4).

$$T_3 = K_1T(a - T) + K_1K_2(2a - T)$$

$$cis\text{-}[PtCl_2(NH_3)_2] \underset{}{\overset{K_1}{\rightleftharpoons}} cis\text{-}[PtCl(OH_2)(NH_3)_2]^+ + Cl^-$$

$$cis\text{-}[PtCl(OH_2)(NH_3)_2]^+ \underset{}{\overset{K_2}{\rightleftharpoons}} cis\text{-}[Pt(OH_2)_2(NH_3)_2]^{2+} + Cl^-$$

---

cis-$[PtCl(OH_2)(NH_3)_2]^+ = x$ $\qquad$ cis-$[Pt(OH_2)_2(NH_3)_2]^{2+} = y$

cis-$[PtCl_2(NH_3)_2] = a - x - y$ $\qquad$ $Cl^- = x + 2y = T$

$$K_1 = \frac{x(x + 2y)}{a - x - y} \qquad K_2 = \frac{y(x + 2y)}{x}$$

$$K_2 = \frac{y(x + 2y)}{x} \qquad \text{also} \qquad y = \frac{T - x}{2}$$

$$= \frac{yT}{x} \qquad K_2 = \frac{(T - x)T}{2x}$$

$$= \frac{yT}{T - 2y} \qquad T^2 = x(2K_2 + T)$$

$$yT = (T - 2y)K_2 \qquad x = \frac{T^2}{2K_2 + T}$$

$$y = \frac{K_2T}{T + {}_2K_2}$$

Now:

$$K_1 = \frac{xT}{a - x - y} = \left(\frac{T^3}{T + 2K_2}\right) \Big/ \left(a - \frac{T_2}{T + 2K_2} - \frac{K_2T}{T + 2K_2}\right)$$

so $\quad T^3 = K_1(aT) + 2K_1K_2a - K_1T^2 - K_1K_2T$

$$= K_1T(a - T) + K_1K_2(2a - T)$$

APPENDIX 3: Supplementary Tables

Table A3.1: Observed and calculated rate constants for the first step in the chloride anation of some $[Pt(N)_2(OH_2)_2]^{2+}$ complexes (I = 1.0 M).

$(N)_2$	T (°C)	$[Cl^-]$ (mM)	$10^4 k_{obs}$ (s^{-1})	$10^2 k_{-2}$[a] ($M^{-1}s^{-1}$)	$10^2 k_{-2}$[b] ($M^{-1}s^{-1}$)	$10^2 k_{-2}$[c] ($M^{-1}s^{-1}$)
cis-$(NH_3)_2$	20.5	18	11.7	6.50	6.28	6.06
		33	17.3	5.24		
		43	30.5	7.09		
	25.0	18	17.3	9.61	9.11	9.27
		23	20.1	8.74		
		33	29.6	8.97		
	30.0	23	35.1	15.3	14.1	14.7
		33	45.4	13.8		
		43	57.2	13.3		
	35.0	18	40.6	22.6	23.3	22.8
		23	53.0	23.4		
		33	79.7	24.2		
		43	98.4	22.9		
	40.0	18	63.5	35.3	35.2	35.0
		23	79.2	34.4		
		33	119	36.0		
cis-$(py)_2$	13.6	2.65	1.71	6.50	6.65	6.05
		5.20	3.90	7.50		
		7.55	4.40	5.80		
		10.2	6.90	6.80		
	20.5	2.65	2.90	10.9	11.4	12.6
		5.20	6.30	12.1		
		7.55	8.50	11.3		
		10.2	11.4	11.1		
	26.0	2.65	6.10	23.0	21.0	22.1
		5.20	11.2	21.5		
		7.55	16.3	21.5		
		10.2	21.3	20.9		
			21.3	20.9		
		13.2	25.9	19.6		
			25.8	19.5		
	32.6	2.65	17.0	32.6	40.1	42.1
			12.4	46.8		
		5.20	20.2	38.8		
		7.55	32.7	43.3		
		10.2	45.2	44.3		
			34.2	33.5		
		13.2	55.0	41.7		
	40.0	2.65	24.3	91.7	80.1	84.4
		5.20	41.8	80.3		
			36.0	69.2		
		7.55	63.0	83.4		
		10.2	78.1	76.0		

en	18.0	23	32.8	14.3	13.7	13.5
		33	44.7	13.5		
		43	57.5	13.4		
	23.2	18	38.5	21.4	20.9	21.1
		23	46.8	20.4		
		33	68.9	20.9		
	30.0	18	67.2	37.3	35.9	36.8
		23	80.4	35.0		
		33	117	35.5		
	35.0	18	104	57.6	55.5	54.7
		23	121	52.7		
		33	185	56.1		
	39.4	23	181	78.8	77.2	76.6
		33	250	75.7		
chxn	15.5	18	13.5	7.50	7.95	8.6
		43	36.2	8.40		
	20.5	23	31.6	13.7	14.5	14.0
		33	49.1	14.9		
		43	65.1	15.1		
	23.6	18	21.6	21.6	19.4	18.6
		23	20.7	20.7		
		33	17.3	17.3		
		43	18.3	18.3		
	30.3	18	33.4	33.4	33.8	34.7
		23	34.2	34.2		
	37.3	18	32.8	62.8	62.9	64.0
		23	63.9	63.9		
		33	62.1	62.1		
tn	18.6	23	34.7	15.1	17.1	18.6
		33	36.6	15.9		
		43	87.6	20.4		
	22.5	18	50.8	28.3	29.6	27.2
		23	69.1	30.1		
		33	101	30.6		
	30.3	18	106	59.1	58.5	56.3
		23	135	58.5		
		33	191	57.9		
	35.0	18	150	83.5	87.5	85.8
		23	205	89.3		
		33	296	89.6		
	39.4	18	219	122	116	126
		23	255	110		
Me_2tn	15.5	33	51.0	15.5	14.8	15.0
		43	60.9	14.2		
	18.4	18	36.9	20.5	19.9	19.2
		23	44.5	19.4		
		33	65.1	19.7		
	23.5	18	53.4	29.7	29.9	29.4
		23	68.1	29.6		
		33	101	30.5		
	30.0	18	81.6	45.0	47.3	49.4
		23	116	50.4		

trans-$(NH_3)_2$	11.8	9.5	50.6	53.0	57.0	56.3
			47.5	50.0		
		11.5	71.4	61.2		
		14.5	88.7	62.1		
		17.0	100	58.8		
	18.0	9.5	90.1	94.8	91.9	90.8
		11.5	104	90.6		
		14.5	133	91.7		
		17.0	154	90.5		
	22.5	9.5	121	127	124	126
		11.5	141	122		
		14.5	177	122		
			181	125		
		17.0	207	122		
			220	129		
	27.0	9.5	161	170	172	175
		11.5	195	170		
		14.5	254	175		
		17.0	298	175		
			294	173		

[a] Calculated from the expression $k_{-2} = k_{obs}[Cl^-]^{-1}$. [b] Mean for entries in Column 5. [c] Calculated from the activation parameters cited in Table 3.1.

Table A3.2: Effect of ionic strength on k_{-1} and k_{-2} for *cis*-$(NH_3)_2$ at 25 °C.

I (M)	$10^4 k_{-1}$[a] ($M^{-1}s^{-1}$)	$10^2 k_{-2}$ ($M^{-1}s^{-1}$)
0.05	79.7	20.5
0.1	76.8	20.2
0.5	-	10.7
1.0	62.6	9.27

[a] Ref. [49].

Table A3.3: Observed and calculated rate constants for the bromide anation of some $[PtBr(N)_2(OH_2)]^+$ complexes (I = 1.0 M).

Complex	T (°C)	$[Br^-]$ (mM)	$10^4 k_{obs}$[a] (s^{-1})	$10^4 k$(calc)[b] (s^{-1})
cis-$(NH_3)_2$	19.3	22.0	4.66	4.68
		36.5	5.31	6.75
		56.5	10.4	9.35
	25.3	22.0	10.2	8.77
		36.5	13.4	11.6
		66.5	15.9	13.4
		72.5	18.8	14.5
		86.5	24.1	17.2
	30.5	22.0	14.3	15.1
		36.5	18.6	19.3
		56.5	23.8	25.2
		66.5	27.7	28.1
		72.5	34.3	30.1
	36.0	36.5	36.4	35.9
		56.5	46.3	45.3
		66.5	52.3	50.5
		72.5	53.6	53.6
		86.5	57.4	60.8
	40.7	9.50	28.1	33.4
		22.0	42.0	41.9
		36.5	51.0	51.8
		66.5	70.3	72.1
		72.5	76.0	76.2
		86.5	86.0	85.7
	45.5	22.0	57.4	60.4
		36.5	71.2	73.9
		66.5	105	102
		86.5	125	120
cis-$(py)_2$	20.9	15.0	13.2	14.4
		40.0	17.3	18.1
		55.0	18.9	20.3
		70.0	21.1	22.5
		85.5	23.7	24.7
	28.8	15.0	26.1	24.7
		25.5	29.0	27.8
		55.0	38.0	32.1
		70.0	42.0	40.1
		85.5	46.7	45.6
	39.4	15.0	44.9	43.9
		25.5	49.5	50.0
		40.0	57.4	58.4
		55.0	66.3	67.0
		70.0	78.2	75.7

		85.5	83.7	84.7
	46.0	15.0	62.2	61.2
		25.5	73.7	72.4
		40.5	93.6	88.4
		55.5	105	104
		70.0	126	120
en	21.7	32.0	18.2	18.9
		67.0	35.3	35.7
		72.5	37.6	38.3
		86.5	45.1	45.0
	25.9	32.0	24.5	28.4
		42.0	33.1	35.4
		67.0	49.3	52.9
		72.5	55.7	56.7
		86.5	65.5	66.6
	31.6	32.0	43.3	45.2
		42.0	50.6	56.2
		67.0	84.9	84.0
		86.5	108	106
	40.8	32.0	87.2	101
		42.0	121	126
		67.0	190	188
		86.5	251	237
chxn	12.3	10.0	10.5	10.1
		30.0	16.5	17.2
		41.5	21.5	21.3
		65.5	24.2	29.9
	19.2	10.0	15.1	16.4
		21.0	21.6	22.3
		30.0	27.2	27.2
		41.5	30.9	33.4
		65.5	44.5	46.4
	24.0	10.0	21.7	24.7
		21.0	34.9	34.8
		30.0	43.9	43.0
		41.0	53.5	53.1
		65.5	74.1	75.5
	29.0	10.0	41.3	37.4
		21.0	52.8	52.7
		30.0	65.6	65.2
		41.0	80.1	80.5
		65.5	115	115
	33.5	10.0	61.3	51.7
		21.0	71.1	72.4
		30.0	92.3	89.2
		41.0	112	110

Me_2tn	13.4	32.0	11.1	12.2
		40.5	15.3	15.1
		55.0	20.5	19.9
		70.0	25.2	24.9
		85.5	30.0	30.1
	18.0	17.5	11.1	12.2
		32.0	19.9	19.4
		40.5	25.8	23.6
		55.0	31.9	30.9
		70.0	39.0	38.4
		85.5	45.8	46.2
	22.7	17.5	19.4	20.2
		32.0	30.1	31.0
		55.0	49.4	48.2
		70.0	60.7	59.4
		85.5	70.8	71.0
	28.0	17.5	37.6	36.7
		32.0	51.7	52.7
		55.0	77.0	78.0
		70.0	87.0	94.5
		85.5	108	117
	33.9	17.5	59.6	62.2
		32.0	85.2	86.4
		55.0	120	125
		70.0	146	150
trans-$(NH_3)_2$	12.4	32.0	17.3	17.1
		43.0	20.6	20.7
		67.0	28.5	28.6
		86.5	35.4	35.1
	19.4	32.0	37.5	36.2
		43.0	45.8	45.3
		67.0	64.0	64.9
		72.5	72.1	69.5
		86.5	80.5	80.9
	25.2	32.0	59.5	59.6
		43.0	72.1	74.2
		67.0	106	106
		72.5	118	113
		86.5	130	132
	30.0	11.5	40.3	43.7
		22.0	57.8	62.6
		22.5	59.2	63.5
		43.0	104	100
	35.0	11.5	59.8	64.9
		22.5	102	102
		31.5	141	132
		43.0	174	170
		67.0	267	251

trans-$(NH_3)_2$[c]	35.5	21.5	10.3	12.9
		36.5	21.9	18.7
		51.5	23.5	24.6
		67.5	31.2	30.8
		82.0	38.7	36.5
	40.5	21.5	21.1	21.9
		36.5	32.6	32.0
		51.5	44.7	42.0
		67.5	50.7	52.7
		82.0	59.6	62.4
	43.8	21.5	27.5	30.7
		36.5	49.3	45.0
		51.5	59.4	59.2
		67.5	73.5	74.4
		82.0	98.6	88.2
	46.5	21.5	31.0	40.3
		36.5	61.1	59.0
		51.5	81.2	77.8
		67.5	99.6	97.8
		82.0	117	116
	51.5	21.5	52.2	65.4
		36.5	91.4	96.9
		51.5	122	128
		67.5	148	161
		82.0	186	191
		82.0	185	191

[a] Based on the mean value from 20 - 30 point-by-point calculations over 2 – 3 half lives. The standard deviation from the mean was usually less than 2 %. [b] Calculated using the expression $k_{obs} = k_1 + k_{-1}[Br^-]$ using the data from Table A3.4. [c] Cl^- anation of *trans*-$[PtCl(OH_2)(NH_3)_2]^+$ at 235 nm, I = 0.1 M.

Table A3.4: Derived and calculated rate constants for the bromide anation of $[PtBr(N)_2(OH_2)]^+$ (I = 1.0 M).

$(N)_2$	T (°C)	10^4k_1[a] (s^{-1})	10^4k_1(calc)[b] (s^{-1})	10^2k_{-1}[a] ($M^{-1}s^{-1}$)	10^2k_{-1}(calc)[c] ($M^{-1}s^{-1}$)
cis-$(NH_3)_2$	19.3	2.0	2.1	1.30	1.25
	25.3	4.5	4.4	1.94	2.04
	30.5	8.6	8.2	2.94	3.10
	36.0	16	15	5.18	4.74
	40.7	27	26	6.78	6.74
	45.5	40	44	9.29	9.54
cis-$(py)_2$	20.9	12	13	1.46	1.48
	28.8	20	20	2.97	2.52
	39.4	35	34	5.78	6.32
	46.0	45	47	10.7	10.2
en	21.7	3.5	3.7	4.80	4.76
	25.9	6.0	5.6	7.00	6.95
	31.6	9.6	9.6	11.1	11.4
	40.8	22	22	24.8	24.5
chxn	12.3	6.5	6.4	3.57	3.36
	19.2	11	11	5.40	6.06
	24.0	16	16	9.14	8.79
	29.0	24	23	139	13.3
	33.5	33	32	18.7	18.8
tn	18.6	2.0	2.2	5.60	5.67
	24.1	6.0	5.3	8.70	8.65
	31.5	16	16	15.2	14.9
	40.7	60	62	27.9	28.3
Me_2tn	13.4	1.5	1.5	3.35	3.37
	18.0	3.4	3.4	5.00	4.99
	22.7	7.8	8.0	7.47	7.33
	28.0	21	20	11.0	11.2
	33.9	33	37	16.7	17.0
trans-$(NH_3)_2$	12.4	6.5	6.6	3.2	3.5
	19.4	10	11	8.4	7.3
	25.2	17	16	13.3	12.9
	30.0	23	21	18.0	20.3
	35.0	27	29	33.4	32.1
trans-$(NH_3)_2$[d]	35.5	0.6	0.6	4.70	4.90
	40.5	1.0	1.0	8.00	8.00
	43.8	1.6	1.5	12.0	11.1

	46.5 51.5	2.0 3.0	1.9 3.2	14.6 21.8	14.4 22.9

[a] Estimated from the expression $k_{obs} = k_1 + k_{-1}[Br^-]$. [b] Calculated from the activation parameters cited in Table 3.5. [c] Calculated from the activation parameters cited in Table 3.4. [d] Data for the chloride anation of *trans*-$[PtCl(OH_2)(NH_3)_2]^+$ (I = 0.1 M).

Table A3.5: Kinetic data for the bromide anation of $[Pt(N)_2(OH_2)_2]^{2+}$ complexes (I = 1.0 M).

$(N)_2$	T (°C)	$[Br^-]$ (mM)	$10^2 k_{obs}$ (s^{-1})	k_{-2}[a] ($M^{-1}s^{-1}$)	k_{-2}[b] ($M^{-1}s^{-1}$)	k_{-2}[c] ($M^{-1}s^{-1}$)
cis-$(NH_3)_2$	18.4	50	1.20	0.24	0.23	0.24
		70.5	1.61	0.23		
		90.5	2.04	0.22		
		107.5	2.43	0.23		
		120	2.84	0.24		
	25.0	50	2.28	0.46	0.45	0.45
		70.5	3.14	0.45		
		91.5	4.10	0.45		
		107.5	4.83	0.45		
	34.5	50	5.72	1.14	1.12	1.07
		70.5	7.74	1.10		
		91.5	10.4	1.13		
		107.5	12.4	1.15		
		120	13.1	1.09		
	43.9	50	11.4	2.28	2.33	2.41
		70.5	16.2	2.30		
		91.5	21.1	2.30		
		107.5	25.9	2.41		
		120	28.1	2.34		
en	24.9	10	1.31	1.31	1.28	1.28
		20	2.57	1.28		
		30	3.8	1.27		
		40	5.17	1.29		
		50	6.34	1.27		
	34.4	10	3.13	3.13	3.17	3.19
		20	6.38	3.19		
		30	9.49	3.16		
		40	12.7	3.19		
		50	16.0	3.19		
	43.8	10	7.09	7.09	7.38	7.46
		20	14.8	7.40		
		30	22.2	7.39		
		40	29.9	7.47		
		50	37.8	7.56		
	50.4	10	13.2	13.2	13.3	13.2
		20	26.6	13.3		
		30	39.2	13.1		
		40	53.6	13.4		
		50	67.7	13.5		
tn	24.7	10	1.82	1.87	1.82	1.81
		20	3.56	1.78		
		30	5.45	1.82		
		40	7.34	1.83		

		50	9.04	1.81		
	34.4	10	4.71	4.71	4.46	4.44
		20	8.92	4.46		
		30	13.1	4.37		
		40	17.1	4.28		
		50	22.5	4.50		
	43.9	10	9.49	9.49	9.75	10.1
		20	20.7	10.4		
		30	27.2	9.06		
		40	38.5	9.62		
		50	51.2	10.3		
	51.4	10	18.9	18.9	19.2	18.8
		20	38.5	19.2		
		30	57.7	19.2		
		40	78.3	19.6		
		50	96.2	19.2		
Me_2tn	24.9	11	1.76	1.58	1.55	1.52
		20	3.12	1.56		
		30	4.66	1.55		
		40	6.13	1.53		
		50	7.77	1.55		
	34.5	11	3.74	3.40	3.39	3.55
		20	6.77	3.38		
		30	9.93	3.31		
		40	13.1	3.27		
		50	18.0	3.60		
	43.9	10	8.41	8.41	7.92	7.75
		11	9.25	8.15		
		20	16.3	7.38		
		30	22.2	7.29		
		40	29.2	7.88		
		50	39.4	8.41		
chxn	24.9	10	1.16	1.16	1.12	1.12
		20	2.21	1.11		
		30	3.31	1.10		
		40	4.44	1.11		
		50	5.64	1.13		
	34.5	10	3.05	3.05	2.80	2.78
		20	5.53	2.77		
		30	8.42	2.81		
		40	11.1	2.78		
		50	13.0	2.61		
	43.0	10	5.59	5.59	5.74	5.94
		20	10.8	5.41		
		30	16.4	5.48		
		40	24.5	6.13		
		50	30. 5	6.09		
	50.0	10	11.4	11.4	11.1	10.8

		20	21.5	10.7		
		30	33.7	11.2		
		40	44.7	11.2		
trans-$(NH_3)_2$	16.6	10	2.05	2.05	2.00	2.12
		20	3.95	1.98		
		30	5.75	1.92		
		40	8.00	2.00		
		50	10.34	2.05		
	24.9	10	4.74	4.74	4.50	4.19
		20	9.31	4.65		
		30	13.46	4.49		
		40	16.67	4.17		
		50	22.15	4.43		
	34.5	10	8.72	8.72	9.20	8.80
		20	18.4	9.22		
		30	28.	9.59		
		40	34.0	8.51		
		50	49. 9	9.98		
	43.5	10	15.1	15.1	16.1	16.9
		20	31.3	15.7		
		30	49.8	16.6		
		40	66.0	16.5		
		50	82.7	16.6		

[a] Calculated from the expression $k_{-2} = k_{obs}[Br^-]^{-1}$. [b] Mean value of the data in Column 5. [c] Calculated from the activation parameters cited in Table 3.6.

Table A3.6: Crystal data and structural refinement for $[PtBr_4(en)]$ (I) and $[PtBr_4(tn)]$ (II).

Crystal Data		
	(I)	(II)
Empirical formula	$C_2H_8Br_4N_2Pt$	$C_3H_{10}Br_4N_2Pt$
Formula weight	574.83	588.86
Crystal system	monoclinic	orthorhombic
Space group	C2/c	Pnma
Unit cell dimensions	a = 10.414(3) Å	a = 12.666(4) Å
	b = 8.356(2) Å	b = 9.789(5) Å
	c = 11.651(9) Å	c = 8.352(3) Å
	a = 90 °	a = 90 °
	b = 112.77(3) °	b = 90 °
	c = 90 °	c = 90 °
Volume	934.8(8) $Å^3$	1035.5(7) $Å^3$
Z	4	4
Density (calc)	4.084 g/cm^3	3.777 g/cm^3
F(000)	1008	1040
Linear absorption coefficient	32.035 mm^{-1}	28.924 mm^{-1}
Temperature (K)	158(2)	158(2)
Data Collection		
	(I)	(II)
Diffractometer	Siemens P4	Siemens P4
Absorption correction (semi-empirical)	From ψ scans	From redundant data
Max. and min. transmission	0.7470 and 0.3654	0.8433 and 0.1581
Reflections collected	1085	1761
Independent reflections	783	527
θ range	3.23 – 24.99	2.92 – 22.48
Range of h, k and l	$-12 \le h \le 3$	$-10 \le h \le 10$
	$0 \le k \le 9$	$-10 \le k \le 10$
	$-13 \le l \le 13$	$0 \le l \le 5$
Refinement		
	(I)	(II)
Method	Full matrix least-squares on F^2	Full matrix least-squares on F^2
Data/restraints/parameters	783/12/42	527/18/52
H-atom refinement	no ref	no ref
Goodness-of-fit on F^2	1.052	1.017
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0680	R_1 = 0.0669
	wR_2 = 0.1534	wR_2 = 0.1621
R indices (all data)	R_1 = 0.0761	R_1 = 0.0872
	wR_2 = 0.1569	wR_2 = 0.1709
Largest diff. of peak and hole	7.155	2.051
	-5.721 e $Å^{-3}$	-3.479 e $Å^{-3}$

Table A3.7: Kinetic data for the pressure dependence on the anation of $[Pt(N)_2(OH_2)_2]^{2+}$ complexes (25 °C, I = 0.1 M).

Reaction	P (MPa)	$10^2 k_{obs}$ [a, c] (s^{-1})	$\ln k_{obs}$	$\Delta V^{\#}$ ($cm^3\ mol^{-1}$)
en + Cl^- (283 nm) [b]	10	2.27	-3.785	-5.27 ± 1.2
		1.97	-3.925	
	30	2.45	-3.709	
	50	2.55	-3.669	
		2.40	-3.729	
	87.5	2.59	-3.655	
		2.50	-3.688	
	115	2.63	-3.640	
	120	2.75	-3.594	
en + Br^- (290 nm) [b]	10	10.1	-2.290	-5.70 ± 0.5
	25	10.7	-2.237	
	50	11.5	-2.159	
	75	12.3	-2.095	
	100	12.7	-2.067	
	120	13.1	-2.035	
cis-$(NH_3)_2$ + Br^- (300 nm) [b]	25	4.97	-3.003	-5.08 ± 0.6
	50	5.34	-2.929	
	75	5.49	-2.903	
	100	5.96	-2.821	
	125	6.01	-2.812	
tn + Br^- (280 nm) [b]	10	13.2	-2.029	-5.82 ± 1.0
	25	15.8	-1.843	
	42	18.0	-1.715	
	72.5	18.5	-1.687	
	102.5	19.8	-1.618	
	130	20.8	-1.571	
tn + Cl^- (273 nm) [b]	25	3.31	-3.410	-7.41 ± 0.3
	52.5	3.59	-3.328	
	75	3.87	-3.251	
	100	4.19	-3.172	
	127.5	4.46	-3.110	

[a] Mean of at least 4 kinetic traces. [b] Wavelength used to monitor the reaction.
[c] $[Cl^-] = [Br^-] = 50$ mM.

Table A3.8: Data for the pressure dependence on the anation of $[Pt(N)_2X(OH_2)]^+$ complexes (25 °C, 0.1 M $HClO_4$).

Complex	P (MPa)	10^2k_{obs} (s^{-1}) [X^-]= 0.5	0.75	1.0	1.25 (M)	10^2k_{-1}[a] ($M^{-1}s^{-1}$)	$\Delta V^{\#}$ ($cm^3\ mol^{-1}$)
en + Cl^-[b]	10	2.49	2.61	2.72	2.07	2.09	-9.4 ± 0.5
(300 nm)[c]	25	2.25	2.72	3.63	5.41	2.24	
	50	2.44	3.00	4.95	5.95	2.42	
	75	2.64	3.08	5.29	6.90	2.62	
	100	2.74	3.14	5.56	8.35	2.70	
	120	3.22	3.36	5.87	8.77	3.30	
en + Br^-	10	-	5.08	6.67	8.46	4.67	-7.43 ± 0.3
(315 nm)[c]	25	4.04	5.69	7.29	8.47	4.97	
	50	4.37	5.97	8.42	9.34	5.55	
	75	4.73	6.38	8.81	10.4	6.00	
	100	4.98	6.81	9.22	10.9	6.50	
	120	5.23	6.91	9.51	11.4	7.20	
cis-$(NH_3)_2$ +	25	1.38	2.14	2.47	2.55	1.47	-10.16 ± 0.4
Br^-	50	1.48	2.32	2.84	3.48	1.65	
(320 nm)[c]	75	1.56	2.34	2.87	3.60	1.86	
	100	1.63	2.52	2.95	3.70	2.10	
	120	1.69	2.62	3.27	3.99	2.24	
tn + Br^-	10	5.43	7.12	9.95	20.5	9.34	-10.4 ± 0.8
(315 nm)[c]	25	6.59	11.1	11.9	21.1	12.0	
	50	7.50	12.4	14.0	23.4	13.5	
	75	8.58	12.6	16.6	26.2	14.7	
	100	9.41	13.2	17.5	27.6	15.2	
	120	9.75	14.3	18.6	29.5	16.4	

[a] Estimated from the slope of k_{obs} *vs* P. [b] Measured at 304 K. [c] Wavelength used to monitor the reaction.

Table A4.1: Kinetic data for the reduction of platinum(IV) complexes by Sn(II) (1.0 M HCl).

Complex	T (°C)	[Sn(II)] (mM)	k_{obs} ($10^4 s^{-1}$)	k_2 [a] ($M^{-1}s^{-1}$)	k_2 [b] (calc) ($M^{-1}s^{-1}$)
$[PtCl_6]^{2-}$ (330 nm) [c]	14.2	0.36	650	181	190
		0.42	791	188	
		0.48	975	203	
	18.3	0.24	529	220	225
		0.31	709	229	
	21.4	0.16	425	266	255
		0.22	556	250	
		0.35	874	250	
cis-$[PtCl_4(NH_3)_2]$ (275 nm) [c]	14.4	0.29	241	83.1	90.5
		0.38	300	78.9	
		0.45	374	83.1	
		0.49	408	83.3	
	19.3	0.19	225	118	123
		0.31	332	107	
		0.34	390	115	
	23.6	0.24	396	165	160
		0.28	476	169	
		0.38	618	163	
trans- $[PtCl_4(NH_3)_2]$ (275 nm) [c]	14.8	0.38	261	68.7	62.6
		0.53	278	52.5	
		0.78	480	61.5	
	20.0	0.41	395	96.3	92.1
		0.46	454	98.7	
		0.56	450	96.4	
	30.0	0.23	376	164	186
		0.41	761	186	
		0.56	1120	200	

[a] Calculated from the expression $k_2 = k_{obs}[Sn(II)]^{-1}$. [b] Calculated from the activation parameters cited in Table 4.1. [c] Wavelength used to monitor the reaction.

Table A4.2: Kinetic data for the reduction of platinum(IV) complexes by ascorbic acid (0.1 M NaCl, pH=4.0).

Complex	T (°C)	$[H_2A]_T$ (mM)	k_{obs} ($10^4 s^{-1}$)	k (calc) [a] ($10^4 s^{-1}$)	k_{et} [b] ($10^3 s^{-1}$)	$10^3 K_{OS}$ [c]
$[PtCl_6]^{2-}$ (350 nm) [d]	14.4	0.78	179	161	50.7	0.61
		1.5	260	239		
		2.4	257	297		
	19.5	0.78	405	329	96	0.67
		1.5	530	481		
		2.4	529	592		
	23.2	0.68	431	447	140	0.69
		1.5	667	712		
		2.3	774	859		
	26.9	0.68	605	629	210	0.63
		1.5	1040	1020		
		2.9	1230	1360		
trans-$[PtCl_4(NH_3)_2]$ (350 nm) [d]	14.2	0.4	30.9	31.4	5.1	4.0
		1.35	42.5	43.0		
		2.16	50.9	45.7		
		2.64	58.1	46.6		
	19.0	1.35	54.3	50.2	6.0	3.8
		2.16	58.4	53.5		
		2.64	66.0	54.6		
	22.8	0.8	45.0	52.3	6.9	3.9
		1.5	57.6	58.9		
		2.25	53.0	61.9		
		3.0	57.0	63.6		
	26.4	1.5	75.0	80.6	9.6	3.5
		2.25	90.0	85.2		
		3.0	80.3	87.7		
	30.5	0.78	96	93.7	11.5	5.7
		1.49	100	103		
		2.25	103	107		
cis- $[PtCl_4(NH_3)_2]$ (330 nm) [d]	14.3	0.78	36.2	34.7	5.7	2.0
		1.49	41.4	42.7		
		2.25	47.9	46.6		
	25.8	1.49	84.6	83.3	10	2.7
		2.25	84.6	89.3		
		3.00	93	92.6		
	30.5	0.78	85	85.4	13	2.3
		1.49	104	103		
		2.25	110	111		
		3.00	115	116		

[a] Calculated from $1/k_{obs} = 1/k_{et} + 1/k_{et}K_{OS}$. [b] From the reciprocal plot k_{et} = (intercept)$^{-1}$. [c] From the reciprocal plot K_{OS} k_{et} = (slope)$^{-1}$. [d] Wavelength used to monitor the reaction.

Table A4.3: Kinetic data for the reduction of platinum(IV) complexes by hydroxylamine (0.1 M NaCl).

Complex	T (°C)	[hyd] (mM)	k_{obs} ($10^4 s^{-1}$)	k (calc) [a] ($10^4 s^{-1}$)	k_{et} [b] ($10^3 s^{-1}$)	K_{OS} [c]
$[PtCl_6]^{2-}$ (350 nm) [d]	35.0	10	6.12	5.92	1.04	132
		27	8.04	8.13		
		6	4.70	4.59		
		30	9.11	8.31		
		6	4.47	4.59		
		15	6.00	6.90		
		21	7.38	7.65		
		11.5	6.83	6.27		
	46.5	62	25.9	23.3	1.53	111
		46	24.5	22.4		
		36	23.2	21.5		
		30	20.3	20.7		
		25	18.8	19.8		
		14	15.6	16.6		
		7	15.9	12.1		
	40.0	10	8.65	8.06	2.63	123
		22	11.2	11.3		
		21	10.8	10.7		
		14	8.47	9.34		
		41	12.1	12.6		
		58.5	12.2	13.3		
		14	8.73	9.34		
		41	11.7	12.6		
trans- $[PtCl_4(NH_3)_2]$ (325 nm) [d]	31.0	46	12.7	5.92	7.66	74.0
		6.5	2.45	2.49		
		56	11.7	6.17		
		25	13.8	4.97		
		12	3.67	3.60		
		20	5.12	4.57		
		70	6.27	6.27		
	37.9	12	6.08	6.48	11.9	99.6
		26	9.15	8.58		
		40	9.48	9.51		
		17	7.46	7.48		
		11	5.70	6.22		
		8	4.92	5.28		
	44.0	19	12.6	12.5	17.4	131
		22.5	14.3	13.0		
		43	14.2	14.8		
		32	12.9	14.0		

		9.5	9.90	9.63		
cis- $[PtCl_4(NH_3)_2]$ (270 nm) [d]	36.0	7	1.13	1.14	3.58	66.5
		15	1.82	1.79		
		40	2.73	2.60		
		24	2.10	2.20		
		20	20.6	2.04		
		11	1.50	1.51		
	46.0	20	5.56	5.68	8.90	88.2
		12	4.96	4.58		
		14.5	4.77	4.99		
		50	7.55	7.25		
		19.5	5.49	5.63		
	52.0	11	9.06	8.08	15.2	104
		30	17.1	17.5		
		15	10.4	9.23		
		12.5	8.96	8.56		
		20	10.9	10.2		
		40	10.9	12.2		
		25	11.1	10.9		

[a] Calculated from $1/k_{obs} = 1/k_{et} + 1/k_{et}K_{OS}$. [b] From the reciprocal plot k_{et} = (intercept)$^{-1}$. [c] From the reciprocal plot $K_{OS}\,k_{et}$ = (slope)$^{-1}$. [d] Wavelength used to monitor the reaction.

Table A4.4 Kinetic data for the reduction of platinum(IV) complexes by iron(II).

Complex	T (°C)	[Fe(II)] (mM)	k_{obs} ($10^4 s^{-1}$)	$10^2 k_2$ [d] ($M^{-1}s^{-1}$)	$10^2{}_2$ (calc) [e] ($M^{-1}s^{-1}$)
$[PtCl_6]^{2-}$ [a] (355 nm) [f]	14.9	5.5	5.9	10.7	11.5
		10.5	10.2	9.7	
		15.5	16.5	10.6	
		20	23.9	12.0	
	20.5	5.5	11.7	21.3	18.7
		10.5	20.2	0.19.2	
		15.5	30.5	19.8	
		20	39.6	19.8	
		25	50.3	20.1	
	27	5.5	20.0	36.4	32.3
		10.5	32.3	30.8	
		15.5	50.2	32.4	
		20	66.3	33.2	
		25	83.0	33.2	
	35	5.5	31.1	56.5	61.0
		10.5	58.9	56.1	
		15.5	93.2	60.1	
$[PtCl_6]^{2-}$ [b] (355 nm) [f]	20	15.5	13.4	8.6	8.7
		20.5	17.6	8.6	
		25.5	22.5	8.8	
		31.0	28.3	9.1	
		35.5	30.4	8.6	
	25.5	15.5	20.2	13.0	13.7
		20.5	28.2	13.8	
		25.5	35.2	13.8	
		31.0	42.0	13.5	
		35.5	50.0	14.1	
	32	5	13.4	26.8	23.1
		15.5	34.8	22.4	
		20.5	45.3	22.1	
		25.5	58.3	22.9	
	37	5.0	19.0	38.0	.34.0
		10.0	32.1	32.1	
		15.5	48.8	31.4	
$[PtCl_6]^{2-}$ [c] (355 nm) [f]	20	15.5	17.8	11.5	11.0
		20.5	22.6	11.0	
		25.5	25.9	10.2	
		30.5	33.9	11.1	
		35.5	37.8	10.6	
	26.5	10.5	18.3	17.4	17.5
		15.5	28.7	18.5	
		20.5	36.5	17.5	

		25.5	44.7	17.5	
		30.5	54.9	18.3	
	33.5	10.5	25.5	24.3	28.1
		15.5	50.9	32.8	
		20.5	58.9	28.7	
		25.5	71.9	28.2	
		30.5	79.6	26.1	
cis-[b] $[PtCl_4(NH_3)_2]$ (380 nm) [f]	40.0	38.5	2.17	56.4	59.8
		46.5	2.81	60.4	
		56	3.28	58.6	
		67	4.12	61.5	
		77.5	4.81	62.0	
	47.0	38.5	5.0	130	126
		46.5	6.34	136	
		56	7.8	139	
		67	9.34	139	
	55.5	36	9.87	274	285
		48	13.4	279	
		60	16.47	275	
		76.5	20.76	271	
trans-$[PtCl_4(NH_3)_2]$[b] (380 nm) [f]	40.7	35.5	2.64	74.4	79.5
		43.5	3.82	87.8	
		50	3.53	70.6	
		59.5	4.63	77.8	
	47.9	59.5	10.5	180	160
		51	8.51	170	
		69	11.0	160	
		35	6.23	180	
		75	11.1	150	
	54.7	36	10.87	300	301
		50	14.25	290	
		64	18.4	290	
		31	9.5	310	
		26	7.2	280	

[a] 0.1 M HCl. [b] 1.0 M HCl. [c] 1.0 M $HClO_4$. [d] Calculated from the expression $k_2 = k_{obs}[Fe(II)]^{-1}$. [e] Calculated from the activation parameters cited in Table 4.4. [f] Wavelength used to monitor the reaction.

Table A4.5: Kinetic data for the reduction of platinum(IV) complexes by thiosulfate (0.1 M NaCl).

Complex	T (°C)	$[S_2O_3^{2-}]$ (mM)	k_{obs} ($10^4 s^{-1}$)	$10^2 k_2$ [a] ($M^{-1}s^{-1}$)	$10^2 k_2$ (calc) [b] ($M^{-1}s^{-1}$)
$[PtCl_6]^{2-}$ [c] (390 nm)[c]	12.0	8	20.1	25.1	26.0
		12.5	29.9	23.9	
		17.5	47.5	27.1	
		22.5	62.2	27.6	
		27.5	78.5	28.5	
	18.5	8	26.4	33.0	38.8
		12.5	49.2	39.4	
		17.5	72.0	41.1	
		22.5	91.4	40.6	
		27.5	107	39.0	
	25.0	8	46.3	57.9	56.7
		8	41.4	51.7	
		12.5	71.1	56.9	
		17.5	100	57.4	
		27.5	150	54.5	
	30.0	8	60.9	76.1	75.1
		12.5	101	80.8	
cis-$[PtCl_4(NH_3)_2]$ (320 nm) [c]	17.8	10	771	771	828
		20	1570	783	
		30.5	2504	821	
		40.5	3330	822	
		51.5	4370	849	
	24.9	10	1606	1610	1560
		20	3255	1630	
		30.5	5098	1670	
		40.5	6835	1690	
		51.5	8343	1630	
	32.4	10	2853	2850	2950
		20	5801	2900	
		30.5	8592	2820	
		40.5	11600	2870	
		51.5	14700	2860	
	40.9	10	5821	5820	5860
		20	11900	5960	
		30.5	17900	5870	
		40.5	23900	5900	
trans-$[PtCl_4(NH_3)_2]$ (350 nm) [c]	25.0	10	1191	1190	1170
		20	2214	1110	
		30.5	3726	1220	
		40.5	4762	1180	

		51.5	6002	1170	
	32.6	10	2114	2110	2180
		20	4464	2230	
		30.5	6501	2130	
		40.5	8918	2200	
		51.5	11000	2140	
	40.8	10	4086	4090	4120
		20	8198	4100	
		30.5	12600	4140	
		40.5	16600	4110	
		51.5	21500	4180	
	47.5	10	6849	6850	6770
		20	13600	6810	
		40.5	27500	6790	

[a] Calculated from the expression $k_2 = k_{obs}[S_2O_3^{2-}]^{-1}$. [b] Calculated from the activation parameters cited in Table 4.5. [c] Wavelength used to monitor the reaction.

Table A5.1: Kinetic data for the oxidation of neutral and positively charged platinum(II) complexes by peroxydisulfate.

Complex	T (°C)	$[S_2O_8^{2-}]$ (mM)	k_{obs} ($10^4 s^{-1}$)	$10^2 k_2$[a] ($M^{-1}s^{-1}$)	$10^2 k_2$(calc)[b] ($M^{-1}s^{-1}$)
cis-$(NH_3)_2$[c] (350 nm)[e]	36	10	5.3	5.3	5.1
		20	10.6	5.3	
		30	15.1	5.0	
		40	20.1	5.0	
		50	23.1	4.6	
	42.8	10	7.12	7.1	7.1
		20	14.0	7.0	
		30	20.9	7.0	
		40	29.4	7.4	
		50	36.1	7.2	
	30.5	10	3.68	3.7	3.8
		20	7.38	3.7	
		30	11.38	3.8	
		40	16.8	4.2	
		50	19.1	3.8	
chxn[c] (331 nm)[e]	25.0	10	11.9	11.9	11.3
		20	24.1	12.1	
		30.8	37.2	12.2	
	19.5	10	7.5	7.5	7.4
		30	21.7	7.2	
		40	28.9	7.2	
		20	13.8	6.9	
	30.5	25	39.0	15.6	16.9
		8.4	13.6	16.2	
		20	33.5	16.8	
		30	51.5	17.2	
carboplatin[d] (350 nm)[e]	22.5	10	16.9	16.9	16.9
		20	32.2	16.1	
		30	50.6	16.9	
		40	70.0	17.5	
	17.5	10	12.2	12.2	11.4
		20	21.5	10.8	
		30	35.6	11.9	
	12	20	14.0	7.0	7.3
		30	21.0	7.0	
		40	31.3	7.8	
		50	39.3	7.9	
$[Pt(NH_3)_4]^{2+}$[c] (275 nm)[e]	10.8	42.5	564.7	133	140
		50	692.6	138	

		61	760.3	125	
		74	1156	156	
		82.5	1257	148	
	18.4	10	188.6	189	196
		20	400.3	200	
		40	689.4	174	
		60	1270	212	
		80	1668	209	
	23.2	7	155.1	221	240
		10	257.6	258	
		25	610.1	244	
		50	1208	241	
		70	1637	234	
$[Pt(en)_2]^{2+}$ [c]	12.3	12.5	526.3	421	440
(275 nm)[e]		22	992.7	451	
		30	1445	482	
		43	1920	446	
		60	2704	451	
	18.0	10	595.2	595	646
		20	1276	638	
		30	1980	660	
		40	2564	641	
		50	2887	577	
	25.1	10	1059	1060	1020
		20	1965	983	
		30	3247	1080	
		40	3976	994	
		50	5401	1080	

[a] Calculated using Equation (5.2). [b] Calculated from the activation parameters cited in Table 5.1.
[c] 1.0 M HCl. [d] 1.0 M $HClO_4$. [e] Wavelength used to monitor the reaction.

Table A5.2: Kinetic parameters for the oxidation of negatively charged platinum(II) complexes by peroxydisulfate (1.0 M HCl).

Complex	T (°C)	$[S_2O_8^{2-}]$ (mM)	k_{obs} ($10^4 Ms^{-1}$)	$10^2 k_o$[a] (s^{-1})	$10^2 k_o$(calc)[b] (s^{-1})
$[Pt(ox)_2]^{2-}$ (285 nm)[c]	13	0.67	2.54	37.9	43.0
		1.0	4.95	49.5	
		1.5	5.72	35.1	
	17	0.25	2.48	99.2	73.0
		0.58	4.61	83.7	
		1.0	6.8	68.2	
		1.5	12.6	83.8	
	22.6	0.25	4.53	181.0	145
		0.5	6.65	133.0	
		1.0	14.0	140.0	
		1.5	24.4	163	
$[PtCl_2(ox)]^{2-}$ (305 nm)[c]	13.0	2	1.8	9.1	10.5
		3.8	3.7	9.7	
		5	6.0	12.0	
		6.5	7.7	11.8	
	17.7	2.5	4.87	19.5	18.6
		4.1	7.1	18.5	
		5.5	10.2	17.3	
	22.5	1.33	4.0	30.1	32.4
		5.4	19.1	354	
$[PtCl_4]^{2-}$ (340 nm)[c]	30.5	10	1.0	1.0	1.2
		20	2.0	1.1	
		30	4.1	1.4	
		40	5.7	1.4	
		50	6.6	1.3	
	36	10	2.2	2.2	2.7
		20	5.8	2.9	
		30	9.0	3.0	
		40	11.5	2.9	
		45	13.2	2.9	
		50	14.0	2.8	
	42.5	10	5.7	5.7	6.3
		15	8.9	6.0	
		20	12.6	6.3	
		25	16.4	6.6	
		35	23.0	6.6	
		40	28.7	7.1	

[a] Calculated using Equation (5.4). [b] Calculated from the activation parameters cited in Table 5.1.
[c] Wavelength used to monitor the reaction.

Table A5.3: Kinetic data for the oxidation of platinum(II) complexes by H_2O_2 (1.0 M $HClO_4$).

Complex	T (°C)	$[H_2O_2]$ (mM)	k_{obs} ($10^4 s^{-1}$)	$10^3 k_2$ [a] ($M^{-1}s^{-1}$)	$10^3 k_2$ (calc) [b] ($M^{-1}s^{-1}$)
carboplatin (315 nm) [c]	25.0	35	7.50	21.4	18.0
		55	10.5	19.1	
		83	15.7	18.9	
		98.5	18.7	19.0	
		112.5	20.9	18.6	
	31.5	45.5	13.4	29.5	28.9
		60	17.6	29.3	
		82.5	23.1	28.0	
		105	29.6	28.2	
		130	36.7	28.2	
	38.0	38.5	18.7	48.6	45.6
		59.5	27.3	45.9	
		89	35.4	39.8	
		100	45.1	45.1	
	19.5	49	5.50	11.0	11.8
		111	12.9	11.6	
		170	19.3	11.4	
		63.5	7.00	11.0	
$[PtCl_4]^{2-}$ (380 nm) [c]	28.5	50	3.24	6.48	6.14
		60	3.90	6.50	
		98	6.10	6.22	
		115	7.33	6.37	
		135	8.00	5.90	
	35.5	40	4.71	11.8	12.5
		60	8.10	13.5	
		80	9.70	12.1	
		88	9.65	11.0	
		132	14.6	11.1	
	42.0	33	7.80	23.6	23.6
		42	10.5	25.0	
		50	12.8	25.6	
		70	16.3	23.3	
		98	21.2	23.6	
$[Pt(en)_2]^{2+}$ (335 nm) [c]	30.0	50	2.91	5.82	5.97
		55	3.01	5.47	
		77	4.96	6.44	
		82.5	5.27	6.39	
		115	7.34	6.38	
	35.0	50	4.37	8.73	9.51
		55	5.18	9.42	

		87	7.90	9.08	
		116	10.8	9.31	
	40.5	51.5	8.33	16.1	15.6
		65.5	10.8	16.5	
		85.5	13.3	15.5	
		100	15.5	15.5	
$[Pt(NH_3)_4]^{2+}$	30.0	60	3.03	5.05	4.98
(335 nm) [c]		83.5	3.9	4.70	
		117.5	5.71	4.86	
		140	7.33	5.24	
		143.5	7.63	5.10	
	36.5	80.5	6.95	8.63	8.83
		91	8.04	8.84	
		128	11.4	8.93	
		138	12.2	8.84	
		146.5	12.74	8.64	
	42.0	62	8.97	14.5	14.1
		79.5	10.3	30.0	
		107.5	15.96	14.9	
		131.5	18.75	14.3	
$[Pt(ox)_2]^{2-}$	12	13.5	7.44	55.1	55. 6
(360 nm) [c]		18.75	10.2	54.5	
		27.5	15.2	55.3	
		38.5	21.3	55.3	
	17.3	15	13.5	90.0	85. 5
		22	18.7	85.0	
		30	25.2	84.0	
		50	44.9	89.8	
	22.1	14	17.5	125	125
		30	37.7	126	
		35	42.0	120	
		45	55.0	122	
cis-$(NH_3)_2$	42	35	9.30	26.6	26.6
(350 nm) [c]		56	15.3	27.3	
		80	20.8	26.0	
		97	25.6	26.4	
		113	30.6	27.0	
	36	30	5.50	18.3	18.4
		50	9.70	19.4	
		65	12.6	19.4	
		75	13.1	17.5	
		116	20.2	17.4	
	31	40	5.61	14.0	13.4
		50	6.10	12.2	
		80	10.7	13.4	
		95	13.0	13.7	
		105	14.3	13.6	

		120	16.2	13.5	
chxn	20.0	27.5	5.82	21.2	22.1
(331 nm) [c]		45.5	9.96	21.9	
		72.5	14.6	20.2	
		90	19.7	21.9	
		140	31.1	22.2	
	15.0	30	4.58	15.3	14.4
		40.5	6.28	15.5	
		64	8.88	13.9	
		83	11.7	14.0	
	25.0	28	10.3	36.8	33.6
		39	13.2	33.8	
		51.5	16.6	32.2	
		62	21.3	34.4	

[a] Calculated using Equation (5.14). [b] Calculated from the activation parameters cited in Table 5.2.
[c] Wavelength used to monitor the reaction.

Table A5.4: Kinetic data for the oxidation of platinum(II) complexes by permanganate (0.1 M $HClO_4$).

Complex	T (°C)	[Pt(II)] (mM)	k_{obs} (s^{-1})	$10^{-3}k_2$[a] ($M^{-1}s^{-1}$)	$10^{-3}k_2$ (calc)[b] ($M^{-1}s^{-1}$)
$[PtCl_4]^{2-}$ (520 nm)[c]	15.6	3.44	77.1	22.4	22.6
		2.31	53.4	23.1	
		1.88	40.4	21.5	
		1.35	30.3	22.4	
		0.96	20.5	21.3	
		0.96	21.7	22.6	
	24.9	0.70	26.7	38.2	34.3
		1.20	44.1	36.8	
		2.19	77.5	35.4	
		1.73	62.3	36.0	
		3.32	109	32.8	
	34.9	0.77	39.3	51.0	52.1
		1.30	65.8	50.6	
		1.73	88.0	50.9	
		2.22	116	52.1	
		3.13	157	50.2	
$[Pt(NH_3)_4]^{2+}$ (520 nm)[c]	15.0	0.71	95.3	134	133
		0.71	95.9	135	
		1.245	167	134	
		1.245	168	135	
		1.865	251	134	
		1.865	250	134	
		3.11	415	133	
		3.11	418	134	
	19.8	0.71	110	155	160
		0.71	110	155	
		1.245	194	155	
		1.245	194	156	
		1.865	289	155	
		1.865	290	156	
		3.11	483	155	
		3.11	485	156	
	25.0	0.71	140	196	194
		0.71	140	196	
		1.245	246	198	
		1.245	244	196	
		1.865	367	197	
		1.865	368	197	
		3.11	611	196	
		3.11	614	197	

$[Pt(en)_2]^{2+}$ (520 nm) [c]	10.5	0.625	149	238	175
		1.25	219	175	
		1.875	328	175	
		3.125	550	176	
	15.5	0.625	136	218	218
		1.25	286	229	
		1.875	402	214	
		3.125	676	216	
	20.2	0.625	169	270	265
		1.25	325	260	
		1.875	504	269	
		3.125	826	264	
	25.0	0.625	203	324	312
		0.625	198	316	
		1.25	408	326	
		1.875	615	328	
		3.125	914	318	
carboplatin (520 nm) [c]	11.0	0.63	35.5	71.1	71.8
		1.26	89.2	70.8	
		1.89	135	71.2	
		3.15	222	70.3	
	14.5	0.63	50.6	80.3	79.3
		1.26	102	81.7	
		1.89	152	80.4	
		3.15	257	81.1	
	19.0	0.63	56.3	89.4	89.8
		1.26	112	89.0	
		1.89	170	89.7	
		3.15	285	90.6	
	23.0	0.63	60.4	95.9	100
		1.26	125	99.0	
		1.89	192	101	
		3.15	322	102	

[a] Calculated using Equation (5.17). [b] Calculated from the activation parameters cited in Table 5.3.
[c] Wavelength used to monitor the reaction.

Table A5.5: Kinetic data for the effect of copper(II) on the rate of oxidation of $[PtCl_4]^{2-}$ by peroxydisulfate (20 mM, 1.0 M HCl).

T (°C)	$[Cu^{2+}]$ (10^4M)	k_{obs} ($10^4 M^{-1}s^{-1}$)	k_{Cu}[a] ($M^{-1}s^{-1}$)	k_{Cu}[b] ($M^{-1}s^{-1}$)	k_{Cu}[c] ($M^{-1}s^{-1}$)
30	0	2.2	-	52.5	51.9
	2.5	4.5	49		
	3	5.8	55		
	4	6.6	60		
	5	7.1	46		
36	0	6	-	107	109
	1.25	9.7	124		
	2	9.7	92.5		
	2.5	11.8	116		
	3	12.5	109		
	4	13.9	99		
	5	16.0	100		
43	0	13	-	255	252
	2.5	26	260		
	3	28	250		
	4	32	240		
	5	40	270		

[a] Calculated from the expression $k_{Cu} = ((k_{obs} - \text{intercept})/[Cu^{2+}])/[S_2O_8^{2-}]$. [b] Mean value of Column 4. [c] Calculated from the activation parameters cited in Table 5.1.

Table 5.6: Kinetic data for the oxidation of platinum(II) complexes by dichromate (I = 1.0 M $HClO_4$).

Complex	T (°C)	k_2[a] ($M^{-1}s^{-1}$)	k_2 (calc)[b] ($M^{-1}s^{-1}$)
carboplatin	14.8	2.63	2.67
	21.1	3.57	3.63
	25.0	4.74	4.37
	29.8	5.19	5.45
$[PtCl_4]^{2-}$	14.6	11.32	11.18
	18.7	12.24	12.55
	23.0	14.45	14.13
	28.0	15.98	16.15
	35.0	19.10	19.32
	39.0	21.60	21.33

[a] Calculated from the slope of k_{obs} *vs* $[Cr_2O_7^{2-}]$ plots. [b] Calculated from the activation parameters cited in Table 5.4.

Table A6.1: Kinetic data for the base hydrolysis of $[PtCl(NH_3)_5]^{3+}$, *trans*-$[PtCl_2(NH_3)_4]^{2+}$ and *trans*-$[PtCl_2(en)_2]^{2+}$ (I = 1.0 M).

Complex	T (°C)	$[OH^-]$ (M)	k_{obs} ($10^4 s^{-1}$)	k_{OH} ($10^3 M^{-1}s^{-1}$)	k_{OH} (calc) ($10^3 M^{-1}s^{-1}$)
trans-$[PtCl_2(NH_3)_4]^{2+}$	37	0.4	3.12	0.78	1.27
		0.6	4.15	1.04	
		0.8	8.87	1.48	
		1.0	12.6	1.26	
	44.2	0.2	6.27	3.14	2.74
		0.4	11.2	2.80	
		0.6	13.9	2.32	
		0.8	23.6	2.95	
	48.5	0.2	8.07	4.04	4.27
		0.6	25.1	4.18	
		0.8	34.9	4.37	
		1.0	43.0	4.30	
	54.2	0.2	15.8	7.89	7.52
		0.4	34.0	8.49	
		0.6	45.0	7.50	
		0.8	60.2	7.52	
		1.0	76.6	7.66	
	59	1.0	83.3	8.33	9.87
trans-$[PtCl_2(en)_2]^{2+}$	35.8	0.4	2.55	6.38	4.35
		0.6	2.69	4.48	
		0.8	2.67	4.58	
		1.0	3.38	3.38	
	42.5	0.4	5.23	13.1	10.4
	46	0.4	7.03	17.6	16.2
		0.6	10.1	16.8	
		0.8	12.4	15.5	
		1.0	15.7	15.7	
	54	0.4	21.8	54.5	56.6
		0.6	31.8	53.1	
		1.0	51.4	51.4	
		0.4	1.78	4.45	
$[PtCl(NH_3)_5]^{3+}$	41.5	0.6	2.41	4.02	4.34
		0.8	3.78	4.10	
		1.0	4.49	4.49	
		0.4	4.49	11.2	11.3
	47.9	0.6	8.10	13.3	
		0.8	8.97	11.2	
		1.0	10.8	10.8	
		0.4	14.8	37.0	39.8
	56.8	0.6	24.9	41.5	
		0.8	31.2	39.0	
		1.0	39.8	39.8	

[a] Calculated from the expression $k_{OH} = k_{obs}/[OH^-]$. [b] Calculated from the activation parameters cited in Table 6.1.

Table A6.2: Kinetic data for the base hydrolysis of *cis*- and *trans*-$[PtCl_4(NH_3)_2]$ (I = 1.0 M).

Complex	T (°C)	$[OH^-]$ (mM)	k_{obs} ($10^4 s^{-1}$)	k_{OH}[a] ($10^3 M^{-1}s^{-1}$)	k_{OH}(calc)[b] ($10^3 M^{-1}s^{-1}$)
cis-$[PtCl_4(NH_3)_2]$	39.9	35	1.86	5.31	5.05
		35	1.95	5.57	
		45	2.07	4.61	
	46.6	25	2.98	11.9	12.3
		34	4.16	11.9	
		45	5.61	12.5	
	50.0	15	2.46	16.4	19.0
	53.0	15	5.09	34.0	27.8
		25	7.59	30.4	
		35	9.13	26.1	
		45	11.4	25.3	
trans-$[PtCl_4(NH_3)_2]$	32.4	70	1.53	2.18	2.04
	34.8	90	1.82	2.02	2.81
	38.5	100	2.93	2.90	4.45
	45.4	10	1.51	15.1	10.8
		30	4.01	13.4	
		50	7.73	15.5	
		70	8.74	12.5	
		90	13.2	14.7	
	50.5	100	23.7	23.7	20.1
	53.0	10	2.86	28.6	27.0
		30	9.47	31.6	
		50	12.0	23.9	
		70	16.1	23.1	
		90	19.8	22.0	
	55.6	10	4.93	49.3	36.5
		30	10.2	34.1	
		50	18.1	36.2	
		70	31.1	35.1	
		90	22.4	32.0	
	57.6	100	58.1	58.1	45.9
	61.5	10	5.08	50.8	71.3
		30	17.7	59.1	

[a] Calculated from the expression $k_{OH} = k_{obs}/[OH^-]$. [b] Calculated from the activation parameters cited in Table 6.1.

Table A6.3: Crystal data and structure refinement for *trans*-$[PtCl_2(en)_2](ZnCl_4)$.

Crystal Data	
Empirical formula	$C_4H_{14}Cl_6N_4PtZn$
Formula weight	591.35
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 14.8584(3) Å
	b = 7.48070(10) Å
	c = 14.5118(3) Å
	$\alpha = 90$ °
	$\beta = 108.2170(10)$ °
	$\gamma = 90$ °
Volume	1532.16(5) $Å^3$
Z	4
Density (calc)	2.564 mg/m^3
F(000)	1104
Linear absorption coefficient	11.712 mm^{-1}
Temperature (K)	-129 K
Data Collection	
Diffractometer	Siemens P4
Absorption correction (semi-empirical)	From redundant data
Reflections collected	5900
Independent reflections	2166
θ range	3.08 to 23.31 °
Range of *h*, *k* and *l*	$-16 \leq h \leq 16$
	$-8 \leq k \leq 7$
	$-16 \leq l \leq 16$
Refinement	
Method	Full matrix least-squares on F^2
Data/restraints/parameters	2166/0/133
H-atom refinement	no ref
Goodness-of-fit on F^2	1.216
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0465$
	$wR_2 = 0.1211$
R indices (all data)	$R_1 = 0.0522$
	$wR_2 = 0.1247$
Largest diff. of peak and hole	2.998 and -3.178 e $Å^{-3}$